Office-Supreme Court, U.S.
FILED
DEC 27 1984
ALEXANDER L. STEVAS,
CLERK

84-1032

No. ——

IN THE

Supreme Court of the United States

OCTOBER TERM, 1984

ALCON LABORATORIES (PUERTO RICO), INC., EDGAR H. SCHOLLMAIER, and LEE D. HANSEN, *Petitioners,*

v.

UNITED STATES OF AMERICA, *Respondent.*

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FIRST CIRCUIT

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QUESTIONS PRESENTED

1. Whether it is contrary to the underlying intent of Congress and the public interest to preclude additional precaution and warning statements in the labeling of products marketed under the "grandfather clause" of the Drug Amendments of 1962, by holding, as the Court of Appeals did, that such post-1962 changes in labeling automatically foreclose the "grandfather" exemption contained in those amendments.

2. Whether proof, through qualified experts, that a drug product was generally recognized as safe on the day immediately preceding the date of enactment of the "grandfather clause" of the Drug Amendments of 1962, is the proper interpretation and application of that clause, rather than holding, as the Court of Appeals did, that the "grandfather" clause requires a determination of actual safety on the date of first marketing of such product.

3. Whether the opinions of qualified experts, based upon their evaluation of clinical investigations reported in the published literature, are sufficient under the previous rulings of this Court to establish general recognition of efficacy pursuant to the definition of "new drug" contained in Section 201(p) of the Federal Food, Drug, and Cosmetic Act, as amended.

4. Whether, as inferred by this Court in *United States* v. *Generix Corporation, et al.*, 103 S.Ct. 1298 (1983), a court and jury may, on the basis of expert testimony, determine that two demonstrably bioequivalent products containing the same active ingredients but slightly different excipients, might under some circumstances be the same "drug".

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ALCON LABORATORIES (PUERTO RICO), INC.,[1] EDGAR H. SCHOLLMAIER, and LEE D. HANSEN, *Petitioners,*

v.

UNITED STATES OF AMERICA, *Respondent.*

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FIRST CIRCUIT

Alcon Laboratories (Puerto Rico), Inc., Edgar H. Schollmaier, and Lee D. Hansen ("Alcon") petition for a writ of certiorari to review the opinion and judgment of the United States Court of Appeals for the First Circuit.

OPINIONS BELOW

The opinion of the court of appeals (App. A, *infra,* 1a-28a) is reported at 745 F.2d 105. The relevant

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[1] Pursuant to Rule 28.1 of the Rules of this Court, the parent companies, non-wholly owned subsidiaries, and affiliates of Alcon Laboratories, (Puerto Rico), Inc. are Alcon Laboratories, Inc. and Nestle S.A.

order of the district court (App. C, *infra,* 30a-37a) is unreported.

JURISDICTION

The judgment of the court of appeals (App. B, *infra,* 29a) was entered on September 27, 1984. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

STATUTES INVOLVED

The relevant statutory provisions are set forth in App. D, *infra,* 38a-41a.

STATEMENT [2]

1. This case involves antiemetic [3] suppositories which were continuously marketed, under the trade name WANS, from 1955 until the decision below. WANS contain two active ingredients, pentobarbitol sodium and pyrilamine maleate,[4] formulated in a polyethylene

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[2] The Joint Appendix and Supplemental Joint Appendix filed below will be filed with the Clerk of this Court. References thereto are "J.A." and "S.J.A.", respectively.

[3] An "antiemetic" is a drug used to control vomiting. The name is derived from the Greek "anti" meaning against and "emetikas" meaning vomiting. *See Dorlands Illustrated Medical Dictionary* 89 (26th ed.).

[4] Section 201(g) of the '38 Act, and as amended, 21 U.S.C. 321 (g), refers to "articles recognized in the United States Pharmacopeia . . . (NSP) . . . or official National Formulary (NF)." USP and NF have recently merged. Both organizations publish monographs for the purpose of establishing compendial standards

glycol base[5] with color additives used for product identification.[6]

During the period from 1960 to 1970, more than four million patients used WANS for the symptomatic treatment of nausea and vomiting.[7]

2. Section 505(a) of the Federal Food, Drug, and Cosmetic Act ("the Act, as amended") 21 U.S.C. 355(a),[8] prohibits introduction into interstate commerce of any "new drug" that has not been approved by the Food and Drug Administration (FDA).

The term "new drug" was defined in Section 201(p) of the '38 Act to mean any drug[9] that was not "generally recognized, among experts qualified by scientific training and experience to evaluate the safety

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and specifications with respect to a product's identity, purity and strength.

The monograph for pentobarbital sodium first appeared in the 1940 edition of USP. (USP XII). The monograph for pyrilamine maleate first appeared in the 1955 edition. (USP XV).

[5] Polyethylene glycol, commonly referred to as "carbowaxes" were first covered by monographs in both the NF(X) and USP (XV) in 1955.

[6] WANS were manufactured in three dosage strengths and therefore color coded with FD&C color additives for the purpose of product identification.

[7] *See* opinion of the Court of Appeals, App. A, *infra*, p. 6a.

[8] Reference to the Federal Food, Drug, and Cosmetic Act ("the Act, as amended"), 21 U.S.C. §§ 301 et seq., are to sections as denominated in the Act, as amended.

[9] The precise meaning of the term, "drug", as used in the Act, as amended was addressed by this Court in *United States* v. *Generix Drug Corporation. et al.*, 103 S.Ct. 1298 (1983).

of drugs, as *safe* for use under the conditions prescribed, recommended, or suggested in the labeling thereof," or a drug that had not been used to a material extent or for a material time under other than experimental conditions.

The Drug Amendments of 1962 ("the '62 Amendments") expanded the definition of a "new drug" to include drugs not generally recognized to be also *effective* for their intended use(s).[10] Congress recognized that in absence of an express exception, drugs then currently marketed without FDA approval on the basis of general recognition of safety might become "new drugs" as defined in the '62 Amendments. It therefore established a category commonly referred to as "old drugs" under the "grandfather" clause.[11]

By its terms, the grandfather clause requires that a manufacturer establish the following:

> (i) The drug must have been commercially sold and available in the United States before October 10, 1962, the effective date of the 1962 Amendments.
>
> (ii) The drug must have been generally recognized as safe on the day immediately preceding enactment, (October 9, 1962).
>
> (iii) The drug must not have been the subject of an approved or pending new drug application or an approved or pending investigational drug exemption.

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[10] Pub. L. No. 87-781, 76 Stat. 784.

[11] *Id.*, § 107(c)(4).

(iv) The drug must be intended solely for use under conditions prescribed, recommended or suggested in its labeling on the day immediately preceding the effective date of the Amendments.[12]

3. Alleging "significant new information" linking WANS to "severe and sometimes fatal reactions", the government initiated four seizure actions[13] against WANS and applied for temporary and permanent injunctive relief in the U.S. District Court of Puerto Rico. Alcon ultimately established that those allegations were "undeniably false." *See* opinion of the Court of Appeals, App. A, *infra*, n. 8 p. 7a.[14]

4. In response to four special interrogatories, the jury found as follows:[15]

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[12] *Supra*, n. 11.

[13] Seizure Action No. 78-1830 (November 27, 1978); Seizure Action No. 80-0243 (January 28, 1980); Seizure Action No. 80-2112 (September 30, 1980); Seizure Action No. 82-0055 (January 11, 1982) J.A. 49.

[14] The government's request for a temporary restraining order was denied by Chief Judge Jose V. Toledo. After the government's second seizure, Judge Juan M. Perez-Gimenez ordered that the then three pending actions against Alcon be consolidated and remanded to the FDA for further administrative proceedings. App. E, *infra*, 42a-48a. The decision of the district court is not reported. The FDA appealed, and in February 1981, the court of appeals reversed the district court and remanded the case for trial. App. F, *infra*, 49a-74a, at p. 74a. The first opinion of the court of appeals is reported at 636 F.2d 876. This Court denied Alcon's petition for certiorari. Pursuant to the order of the Court of Appeals, the consolidated cases were tried before a jury. The trial consumed the better part of two weeks including seven days before the jury.

[15] App. G, *infra*, 75a-77a. J.A. 642.

(i) WANS were generally recognized by qualified experts as being safe for their intended use before enactment of the '62 Amendments;

(ii) WANS are presently generally recognized by qualified experts as being safe for their intended use;

(iii) WANS are presently labeled for the same indications and conditions of use as they were before enactment of the '62 Amendments; and,

(iv) WANS are presently generally recognized by qualified experts to be also effective for their intended use.

Applying those findings to the relevant substantive law, the district court held that (i) WANS were not "new drugs" within the meaning of § 201(p) of the Act[16] prior to the effective date of the Drug Amendments of 1962;[17] (ii) WANS were exempted by Congress from those amendments under the "grandfather" clause;[18] and (iii) alternatively, WANS are not "new drugs" within the meaning of § 201(p) as amended in 1962[19] because WANS are generally recognized to be both safe and effective.

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[16] Before enactment of the Drug Amendments of 1962, a drug which was generally recognized by qualified experts as being *safe*, was not a "new drug".

[17] Pub. L. 87-781, 76 Stat. 780 (1962).

[18] *Id.*, § 107(c)(4).

[19] The jury's answer to interrogatory no. 1 is in support of and relevant to the district court's holding (i); answers to interrogatories nos. 1, 2 and 3 are in support of and relevant to the district court's holding (ii); and answers to interrogatories nos. 2 and 4 are in support of and relevant to the district court's holding (iii).

5. The government sought but was denied judgment notwithstanding the verdict.[20] On appeal, the court of appeals concluded, "as a matter of law", that:

> (i) WANS are not presently "intended solely for use under conditions prescribed, recommended or suggested in the labeling thereof"[21] as was in use prior to the effective date of the '62 Amendments, and therefore did not come within the grandfather clause;
>
> (ii) WANS could not ever be generally recognized by qualified experts as being safe for their intended use;[22] and,
>
> (iii) WANS can not be generally recognized by qualified experts to be effective for their intended use.[23]

Based upon its own findings of fact and conclusions of law, the Court of Appeals reversed the judgment on the verdict and instructed the district court to enter judgment for the government.

REASONS FOR GRANTING THE PETITION

This case presents important questions concerning (i) the public's health and safety; (ii) the proper construction and application of the definition of "new drug" under the '38 Act, and the grandfather clause of the Drug Amendments of 1962; (iii) the determina-

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[20] App. C, *infra*, 30a-37a. J.A. 641.

[21] Pub. L. No. 87-781, *supra*, § 107(c)(4); App. A, *infra*, p. 20a.

[22] App. A, *infra*, p. 19a.

[23] App. A, *infra*, p. 28a.

tion of general recognition of efficacy under the definition of "new drug"; and, (iv) the determination of bioequivalency under this court's recent decision in *United States* v. *Generix Drug Corporation, et al.*, 103 S.Ct. 1298 (1983).

The case presents this Court with an opportunity to establish guideposts for trial of cases under a complex regulatory system that allows some products, but not others, to be marketed without pre-market approval by the FDA.

This case concerns far more than the one product immediately at issue. According to public statements of officials of the FDA, as reported in *Scrip* World Pharmaceutical News, it is estimated "that between 10% and 15% of all marketed drug products are in WANS' [Alcon's products] category . . ." App. H, *infra,* 78a-79a. A 1,526-page list of products marketed without the FDA's express approval, including products in the WANS category, has become available only recently. Moreover, approximately twenty-five of the "Top 200" most widely prescribed drug products, exclusive of antibiotics, topical preparations and "DESI Related" drugs are presently marketed without FDA's express approval. *See* Food and Drug Administration Compliance Policy Guide 7132c.01. App. I, *infra,* 80a-88a.

Congress has exercised its oversight of drug regulation since enactment of the Pure Food and Drugs Act of 1906.[24] At no time, however, has Congress required that all drugs be approved by the FDA in order to protect the public's health and safety.[25] Thus, if one

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[24] S.88, 59th Cong. 2nd Sess. (1906).

[25] There are both scientific and practical reasons why Congress has never insisted that all drugs be approved by the FDA. Recognizing the value of actual clinical experience with drug products,

accepts the view of Congress, as well as the regulatory scheme which it enacted, the issues here presented cannot be disposed of—as did the First Circuit—by merely finding a way to hold that a drug not approved by the FDA must come off the market.

Accordingly, review should be granted for the following reasons:

(i) The First Circuit has ruled that a change in labeling which adds additional warnings and precautions automatically takes the product out of "grandfather" status. That interpretation of the grandfather clause can only serve to discourage drug manufacturers of grandfathered products from reflecting new information concerning their product's potential side effects. [LABELING OF "GRANDFATHERED" PRODUCTS, *infra*, p. 10]

(ii) The Court of Appeals ruled that proof of *actual* safety on the *date of first marketing* is the test to be applied under the grandfather clause. That view is in direct conflict with the language of the clause which requires proof of *general recognition* of safety "on the day immediately preceding the *date of enactment*" [of the clause, i.e.,

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Congress has never chosen to deny the significance of medical and scientific knowledge obtained through the ultimate test of any drug, i.e. the use of an established product "to a material extent or for a material time." *See* § 201(p), the Act, as amended. From the legislative history, it is clear that Congress wanted the public to have the best of both worlds, i.e. (i) drugs with well established track records; and, (ii) drug innovation coupled with appropriate safeguards through laboratory and clinical testing.

October 10, 1962]. [GENERAL RECOGNITION OF SAFETY, *infra*, p. 16.]

(iii) The decision below presents a conflict among the circuits with respect to the criterion to be employed in the determination of general recognition of the efficacy of drug products [GENERAL RECOGNITION OF EFFICACY, *infra*, p. 20.]

(iv) The decision below expressly calls into question this Court's closing inference in *Generix*. [GENERIX, *infra*, p. 26.]

LABELING OF "GRANDFATHERED" PRODUCTS

a. The opinion below is of profound consequence because it uproots every conceivable notion of social responsibility with respect to the labeling of drug products marketed under the "grandfather" clause.

Section 107(c)(4) of the '62 Amendments[26] (the "grandfather" clause) provides in relevant part that a grandfathered drug must be "intended solely for use under conditions prescribed, recommended, or suggested" in its labeling prior to the effective date of enactment.[27] The Court of Appeals interpreted that clause as follows:[28]

> "It must be noted that the operative term in the statutory language appears to be 'conditions' not 'use.' We read the language to mean that even

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[26] *Supra*, n. 11.

[27] App. D, *infra*, p. 39a.

[28] App. A, p. 18a.

> if particular *uses* of a drug are the same, a change in the suggested *conditions* for its use will suffice to remove the drug from the protection of the grandfather clause."

After reviewing the additional warnings and precautions that were added to WANS' labeling, the court concluded as follows:[29]

> "The new conditions now suggested for use of WANS in the treatment of nausea and vomiting are sufficient to take WANS out of the grandfather clause and place it squarely within the requirements of the Act as amended."

Conceding that WANS were intended for the "suppression" of nausea and vomiting in the pre-'62 amendments labels,[30] while erroneously confusing the package insert with a promotional piece,[31] the court below ruled that new information included in a product's labeling for the protection of the public's health and safety takes the product out of the grandfather clause. To agree that such a rule of law is consistent with the public interest, is utterly beyond intellectual analysis.[32]

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[29] App. A, p. 19a.

[30] App. A, p. 17a.

[31] The package insert as was in use in 1962 stated that WANS were indicated for the "prevention as well as control of nausea and/or vomiting *regardless of emetic stimuli*" (Emphasis added.) App. J, *infra*, p. 89a.

[32] The addition of warnings and precautions can hardly be interpreted as an *expansion* of the grandfather clause. On the contrary, the function of the labeling in question was to *restrict* uses of the products.

b. The legislative purpose of the grandfather clause, and intent of Congress as to how it should be applied, are abundantly clear. Reporting the Bill to the Senate, Senator Eastland, Chairman of the Senate Judiciary Committee, explained the reason for and purpose of the grandfather clause as follows:

> "As a result of the change in definition of "new drug" and the addition of the new effectiveness test, it is necessary to include transitional provisions. Under these provisions, the new effectiveness test, in the case of drugs previously cleared under a new drug application, will apply only to new or amended claims unless the application is withdrawn or suspended. Withdrawal on the grounds of a lack of substantial evidence of effectiveness will not apply, for a period of 2 years, to existing claims, unless the approval of any of the claims is withdrawn on other grounds. Established drugs which have never been required to go through new drug procedures will not be affected by the new effectiveness test *insofar as their existing claims are concerned.*" (emphasis added). 108 Cong. Rec. 17,366 (August 23, 1962).

There can be no doubt that the intent of Congress was to forestall any unapproved *new claim* for a grandfathered drug. Quite clearly, Congress never intended to prohibit *new warnings. See* Senate Report by Committee on the Judiciary to Accompany Additional Amendments Incorporated in Drug Amendments of 1962, Pub. L. 87-781, 76 Stat. 780 (1962).

In rewriting the "grandfather" clause, the court below has ruled that the intended "use" of a drug is not controlling but that the "conditions" pertaining to when a drug should *not* be used[33] is what

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[33] *Supra*, p. 11.

Congress meant to provide. Such an interpretation is clearly erroneous. The word "conditions", as used in the statute can have only the meaning as explained to the Senate by Senator Eastland's committee report. Obviously, neither the manufacturer nor the physician can or would "prescribe, recommend or suggest" adverse side effects, warnings or precautions. The word "conditions" as used in the statute, is expressly used in the context of "prescribing, recommending or suggesting" a *use* of the drug; not when a drug should not be used because of adverse side effects, warnings or precautions.

The reasoning of the court below cannot be reconciled with either the intent of Congress or the interest of the public. For example, can it be argued seriously that in 1962, Congress deliberately enacted legislation intended to deny from the prescribing physician any newly discovered information which might be of assistance in the treatment and cure of the general public?

The court's decision also runs directly counter to the common law duty of a drug manufacturer to constantly monitor a product's potential for unforeseen side effects and update its labeling as relevant new information is received. The "duty to warn" rule was well established in American jurisprudence before enactment of the '62 Amendments and should therefore be harmoniously integrated into the courts' interpretation of the Act, as amended. The court below has, in effect, ruled that Congress abrogated this rule as it applies to grandfathered products.[34]

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[34] Long before the passage of the '38 Act, the courts had imposed upon manufacturers of drugs and other potentially dangerous

c. Totally aside from the clear language of the grandfather clause, the decision below is in direct conflict with the FDA's regulations pertaining to the labeling of prescription drugs. On April 7, 1975, the FDA published proposed amendments to its regulations governing the labeling of prescription drugs.[35] The objective of that proposal was stated as follows:

> "The primary objective of prescription drug labeling is to provide the essential information the practitioner needs to use the drug safely and effectively in the care of patients. After reviewing whether this objective is being met, the Commissioner of Food and Drugs has determined that

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products the duty to warn of unforeseen side effects and to update those warnings as required. *See, e.g., Gerkin* v. *Brown and Sehler Co.*, 177 Mich. 45, 143 N.W.48 (1913); *Halloran* v. *Parke, Davis & Co.*, 280 N.Y. Supp. 58, 245 A.D. 727 (1935); *Abbott Laboratories, Inc.* v. *Lapp*, 78 F.2d 170 (7th Cir. 1935). This doctrine has continued to develop since the passage of the '38 Act. *See McEwen* v. *Ortho Pharmaceutical Corp.*, 528 P.3d 522 (Or. 1974) (drug manufacturer has a "continuous duty . . . to keep abreast of scientific developments touching upon the manufacturer's product and to notify the medical profession of any additional side effects discovered from its use," quoting *Schenebech* v. *Sterling Drug, Inc.*, 423 F.2d 919, 922 (8th Cir. 1970)). The manufacturer's continuing duty to warn of potential side effects, like the Act, is intended to result in the presence of safer, better drugs in the marketplace. The ruling below pits the Act against the common law duty to warn. Manufacturers of grandfathered drugs have far less incentive to provide updated warnings when by doing so they expose themselves to the risk that such warnings will transform grandfathered drugs into "new drugs." Congress surely did not intend for the Act to provide such disincentives to disclosure and thereby possibly put the public's health at risk.

[35] 40 Fed. Reg. 15391 (1975) p. 15393 (to be codified at 21 CFR Parts 1,3).

> significant improvements can and should be made in drug labeling."

In that notice, the FDA also stated that compliance with the proposed amendments would not "establish new regulatory requirements", e.g. converting a grandfathered drug to a "new drug" requiring FDA's approval, the purpose being,

> "to provide standards so that all package inserts can be brought up to the level of the best ones written in the past."[36]

Noting that "[A]dvances in medical knowledge and practice inevitably precede labeling revisions . . .", the notice further stated what the court below ignored, to wit:

> "The Commissioner concludes that it is essential to the safe use of a drug for the physician to know all adverse effects that are likely to occur with a drug."

Under the proposed amendments, the intended uses of a drug, previously referred to as "indications" was changed to read as follows:

> "(3) *Indications and usage.* (i) Under this section heading, the labeling shall state explicitly:
>
> (a) That the drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, . . .

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[36] The FDA has consistently maintained that its labeling regulations apply to non-approved prescription drugs such as WANS. In this regard, a totally different issue has been raised with respect to the possibility of misbranding as such pertains to efficacy. *See* 44 Fed. Reg. 37434 (1979) at pp. 37443-37444. (Follow-up notice to that appearing in 40 Fed. Reg. 15392 (1975). *Id.*

> (b) That the drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, ...
>
> (c) That the drug is indicated for the relief of symptoms associated with a disease or syndrome, . . ."

As is the custom of Alcon, it commenced relabeling its products in conformity with the amendments as proposed in 1975. It was apparent that the above stated alternative (c) under "Indications and usage" applied to WANS. Thus, the most recent package insert reviewed by the court below was that as rewritten in accordance with the FDA's revised labeling requirements. App. K, *infra,* 91a-98a. Final amendments were published on June 26, 1979. 44 FR 37434 (1979). See 21 CFR 201.57.

Now, the manufacturer of grandfathered drugs is left with equally undesirable alternatives, i.e. either the FDA's regulations with respect to the labeling of prescription drugs are inapplicable or, the opinion of the court of appeals must be ignored. Clearly they cannot be reconciled. Equally certain is the conclusion that the opinion of the court below should not be allowed to remain undisturbed.

GENERAL RECOGNITION OF SAFETY

a. Relying principally on *Weinberger* v. *Hynson, Westcott & Dunning, Inc.,* 412 U.S. 609 (1973), the court below erroneously extrapolated the "substantial evidence" test for efficacy to the determination of the actual safety of WANS. It should be noted at the outset that *Hynson's* applicability to the issues here discussed is inherently limited to dictum.

In *Hynson,* the manufacturer had filed for and obtained an NDA under the '38 Act.[37] Thus, it is clear that the issue of general recognition of safety was not involved because "general recognition" applies only to drugs not covered by an NDA. Holding that the existence of an effective pre-amendment NDA automatically excluded the grandfather clause,[38] this Court's decision turned on questions related principally to the post-amendment requirements with respect to efficacy. This court did not, and had no reason to discuss the requirements for establishing general recognition of safety. A similar analysis is also applicable to *Weinberger* v. *Bentex Pharmaceuticals, Inc.,* 412 U.S. 645 (1973). Thus, neither *Hynson* nor *Bentex* is decisional authority for the ruling of the court below with respect to general recognition of safety under the grandfather clause.

The third case referred to by the court below, *United States* v. *41 Cases, More or Less,* 420 F.2d 1126 (5th Cir. 1970), involved two products used in medicated feed for poultry. The jury's findings were adverse to both products. Here, the jury found for Alcon on the basis of an abundance of expert testimony directed to the criterion established by Congress. Accordingly, there is no basis in law or fact for setting aside those findings.

b. Contrary to the observatons of the court below,[39] the "newness" of a drug is not determined by historical fact or inference. The concept of "new drug" or "old drug" is statutory, not anecdotal. As noted by

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[37] 412 U.S. 615.

[38] *Id.* at 633.

[39] *See,* App. A, *infra,* 6a.

this Court in *United States* v. *An Article of Drug . . . Bacto-Unidisk,* 394 U.S. 784, 793 (1969); the definitions contained in the Act are "term[s] of art."

Contrary to the rulings of this Court and other Circuits, the court below concluded that WANS were "new drugs" in 1955 (App. A, *infra,* p. 6a) because, Alcon's expert witness, Dr. Crawford stated, WANS "were new drugs to us [practicing physicians] in 1956." [App. A, *infra,* n. 5, p. 6a] The Court's finding of "newness" under § 201(p) of the '38 Act is totally unsupportable as a matter of law. *United States* v. *Articles of Drug (Lannett),* 585 F.2d 575 (3d Cir. 1978) *rehearing denied en banc.*

c. The irrelevance of the court's finding with respect to "newness" is best demonstrated by the applicable statutory language. Section 107(c)(4)(B) expressly provides that the grandfather clause is applicable only to a drug which, on the day before enactment, "was not a new drug as defined by § 201(p) of the basic Act as then in force" ('38 Act), because the drug was *generally recognized* to be safe. Thus, neither the issue of *newness* in 1955, nor the issue of *actual* safety in 1962 was the test prescribed by Congress. Citing *Premo Pharmaceutical Laboratories, Inc.* v. *United States,* 629 F.2d 795 (2nd Cir. 1980), the government vigorously argued in its brief to the Court of Appeals that: "The actual safety and effectiveness of the WANS products was not an issue. and the jury was so instructed." The government even argued that the admission of testimony by the FDA's medical officer assigned to WANS was reversible error. (App. L, *infra,* 99a) The Court of Appeals nevertheless held that proof of *actual safety* was the test under the grandfather clause and that the jury's finding of

general recognition of safety was of no consequence, "as a matter of law." (App. A, *infra,* 19a) It has always been Alcon's position that some proof of actual safety is a necessary predicate to the establishment of "general recognition" thereof; but, Alcon has always agreed that proof of "general recognition" of safety is the ultimate issue. *Premo,* p. 804.

Congress established an absolute point in time with respect to whether a drug was, or was not, to be deemed a "new drug" coming within the purview of the new efficacy requirements of the Drug Amendments of 1962. That precise point in time was stated to be "the day immediately preceding the enactment date" of the amendments. Sec. 107(c)(4), *supra,* n. 11.[40] Although a significant amount of Alcon's expert testimony was focused on the test established by Congress, the opinion of the court below never so much as mentions Alcon's proof of general recognition of safety on "the day immediately preceding the enactment date" of the amendments.[41]

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[40] Sec. 107(c)(4) specifically refers to § 201(p) which defines "general recognition".

[41] The concern expressed by the court below with respect to the possibility of subverting the overall intent of the Act is misplaced. It should be readily apparent that in view of the fact that the active and inactive ingredients of WANS were derived from the USP and NF monographs, a great deal of pharmacological information was available to the manufacturer before the products were ever marketed.

GENERAL RECOGNITION OF EFFICACY

In setting aside the jury's verdict with respect to general recognition of efficacy, the Court of Appeals, among other things:

A. Set itself apart from the rulings of the other Circuits;

B. Disavowed its first opinion;

C. Departed from its own rulings with respect to appellate review; and,

D. Ignored the applicable Federal Rules of Evidence.

a) *Conflicts with Other Circuits.* Most Circuits now agree that:

(i) The term "generally recognized", as used in § 201(p) of the Act, should not be equated to "universally recognized"; therefore, the mere existence of a dispute among qualified experts does not automatically require a finding for the government as a matter of law. *United States* v. *Articles of Food and Drug Consisting of Colitrol 80, etc.*, 518 F.2d 743, 746 (5th Cir. 1975); *United States* v. *X-Otag Plus Tablets*, 441 F. Supp. 105, 110 (D. Colo. 1977), *remanded*, 602 F.2d 1387 (10th Cir. 1979); *United States* v. *7 Cartons More or Less . . . Ferro-Lac*, 293 F. Supp. 660 (S.D. Ill. 1968), *aff'd in part and vacated in part*, 424 F.2d 1364 (7th Cir. 1970); *United States* v. *An Article of Drug Neo-Terramycin*, 540 F. Supp. 363, 374-75 (N.D. Tex. 1982); *AMP, Inc.* v. *Gardner*, 389 F.2d 825, 831 (2nd Cir. 1368), *cert. denied*, 393 U.S. 825 (1969), *reh. denied*, 395 U.S. 917 (1969); *United States* v. *41 Cases, More or Less*, 420 F.2d 1126 (5th Cir. 1970); *Lemmon Pharmacal Co.* v. *Richardson*, 319 F. Supp. 375, 378 (E.D. Pa. 1970).

In *Alcon,* the Court stated the following: "Likewise, the government might have sought judgment as a matter of law, as to its claim that any genuine dispute between qualified experts is enough to preclude a finding of general recognition of safety or efficacy." (App. A, *infra,* 10a.) In order to justify its decision to set aside the jury's verdict, however, the Court held that Alcon's evidence was insufficient, as a matter of law, to establish a genuine dispute. (App. A, *infra,* 15a.)

(ii) The term "substantial evidence" as used in § 505(d) of the Act as amended, does not mean proof beyond a reasonable and commonly accepted understanding of that term as used within the context of the Act. *United States* v. *Articles of Food and Drug Consisting of Colitrol 80, etc.,* 518 F.2d 743 (5th Cir. 1975).

Contrary to § 505(d), *Hynson, supra,* p. 16, *Bentex, supra,* p. 17, and the decisions thereunder, the court below held that ". . . Alcon failed to introduce the type of 'substantial evidence' of effectiveness required by the Act as a matter of law." (App. A, *infra,* 26a.) The Court's ruling thus preempts expert opinion called for by § 505(d) of the Act, where the term "substantial evidence" is defined to mean "evidence consisting of adequate and well controlled investigations, . . . on the basis of which it could fairly and reasonably be concluded by . . . *experts* that the drug will have the effect . . . represented . . . in the . . . labeling thereof." (Emphasis added.) (App. D, p. 40a.)

(iii) The term "adequate and well controlled investigations" as used in § 505(d) of the Act, is directed to the necessary predicate upon which scientific ex-

perts—*not the courts*—might responsibly conclude that a drug is effective. *Premo Pharmaceutical Laboratories, Inc.* v. *U.S.*, 629 F.2d 795 (1980) at p. 803 citing *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973) at p. 652. The court below held that, (i) irrespective of § 505(d) of the Act, *Hynson, Bentex* and other court decisions, it could and did find that the published studies relied on by Alcon were not "adequate and well controlled", as a matter of law; (App. A, *infra*, 27a) therefore, (ii) there was no need for a factual inquiry into the general recognition among experts as to WANS' safety and effectiveness. (App. A, *infra*, 27a.) Thus, under *Alcon, it will be left to the courts, rather than qualified experts,* to determine whether clinical trials reported in the published literature are "adequate and well controlled".

b) *The First Opinion.* In its first opinion, the Court of Appeals advised the trial court that, "the FDA carries the burden of proving its position at time of trial." *United States* v. *Alcon Laboratories, etc. et al.*, 636 F.2d 876, p. 888 (1st Cir. 1981). (App. F, 72a.) Pursuant to that opinion and §§ 201(p) and 505(d) of the Act, as amended; in accordance with the teachings of *Hynson*[42] and subsequent cases;[43] in reliance on Rules 702, 703, 704 and 705 of the Federal Rules of Evidence; and, in anticipation of the ruling of this Court in *Generix*,[44] Alcon put on its case with respect to general recognition of the efficacy of WANS.

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[42] *Supra*, p. 16.

[43] *Supra*, p. 20.

[44] *Supra*, p. 8.

In so doing, Alcon introduced three clinical studies reported in the published literature. Those studies were conducted with an equivalent drug product marketed under the trade, "Emerserts." Alcon also produced evidence with respect to the bioequivalence between WANS and Emerserts.[45] Two of the studies relied upon were conducted in children; the third was conducted in adults undergoing surgery.

The design, purpose and quality and conclusions of the studies were thoroughly reviewed with the jury by three of Alcon's expert witnesses, Drs. Brown, Kalman and Bettman, a team of eminently qualified experts associated with the Stanford School of Medicine. Dr. Brown, the biostatistician, Dr. Bettman, the surgeon, and Dr. Kalman, the pharmacologist, all testified that in their opinion, those studies were "adequate and well-controlled" and provided the basis for fairly and responsibly concluding that WANS are recognized as effective for their intended use; that in their expert opinions WANS are generally so recognized; and, that they knew of no event, circumstance or publication which would cast doubt upon or otherwise bring into question the quality of the studies reported and the conclusions derived therefrom.

c) *Standard of Review.* In speculating on the thought processes and credibility of Dr. Kalman (App. A, p. 24a), and quoting totally out of context the testimony of Dr. Brown (App. A, p. 26a), the court below reached well beyond its own guidelines for judicial

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[45] It is Alcon's position that for purposes of meeting the requirements of general recognition of efficacy, Emerserts and WANS should be treated as the same drug. *Infra,* p. 26.

review.[46] The Court of Appeals has previously held that neither the trial nor appellate court is to sit as the seventh or thirteenth juror, *Borras* v. *Sea-Land Service, Inc.*, 585 F.2d 881, 887 (1st Cir. 1978), and mere disagreement with the jury's verdict will not support setting it aside. *Keeler* v. *Hewitt*, 697 F.2d 8, 11 (1st Cir. 1982). Instead, evaluations of the credibility of witnesses or the weight of the evidence presented are to be left to the jury. *Hubbard* v. *Faros Fisheries, Inc.*, 626 F.2d 196, 199 (1st Cir. 1980); *Austin* v. *Unarco Industries*, 705 F.2d (1st Cir.), *cert. dismissed*, 104 S. Ct. 34 (1983).

d) *Federal Rules of Evidence.* The applicable rules of evidence were not even discussed by the court below. It is, however, "black letter law" that an expert may rely on facts or data not admissible in evidence (R. 703) in the giving of an opinion or inference embracing an ultimate issue of fact (R. 704); and, the expert need not disclose the basis upon which the opinion or inference is predicated unless so ordered by the court or asked to do so on cross-examination (R. 705).

The rationale of the foregoing was succinctly stated in Notes of Advisory Committee on Proposed Rules as follows:

> "The basic approach to opinions, lay and expert, in these rules is to admit them when helpful to the trier of fact. In order to render this approach fully effective and to allay any doubt on the sub-

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[46] The cumulative effect of the Court of Appeals' review of Alcon's case suggests that *trial de novo* may be the new direction of appellate review in the First Circuit.

> ject, the so-called 'ultimate issue' rule is specifically abolished by the instant rule."[47]
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> * * *
>
> While the rule allows counsel to make disclosure of the underlying facts or data, as a preliminary to the giving of an expert opinion, if he chooses, the instances in which he is required to do so are reduced. This is true whether the expert bases his opinion on data furnished him at secondhand or observed by him at first hand.[48]

Dr. Kalman testified with respect to the bioequivalency between WANS and Emerserts, and why the studies conducted with Emerserts were applicable to WANS. *None of the testimony by Dr. Kalman on the issue of bioequivalency between WANS and Emerserts is rebutted.*[49] Moreover, on cross-examination, the government did not question Dr. Kalman on the issue of bioequivalency.

A well reasoned and precise statement of opinion in response to the question presented, subject to cross-examination, should have been accepted by the Court of Appeals, as a matter of law, to the same extent as was done by the jury, as a matter of fact. In its second opinion, the Court of Appeals not only ignored its first opinion, but refused to properly consider Alcon's unrebutted testimony, and set aside, "as a matter of law," the jury's finding with respect to general recognition of efficacy.

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[47] Notes to Rule 704, Fed. R. Evid.

[48] Note to Rule 705, Fed. R. Evid.

[49] The government offered *no evidence* specifically questioning the bioequivalency between WANS and Emerserts.

GENERIX

The issue of bioequivalence between WANS and Emerserts is a "first cousin" to *Generix*.[50] In contemplation of this Court's ruling in *Generix*, which came down after the trial of WANS was concluded, Alcon made its case based upon the active and inactive ingredients of WANS and Emerserts. By simply refusing to recognize Alcon's proof,[51] the court below avoided reaching the closing paragraph of this Court's opinion in *Generix* which is as follows:

> "We thus do not reach the issue of whether two demonstrably bioequivalent products containing the same active ingredients but different excipients, might under some circumstances be the same 'drug' ".[52]

The court below appears to treat this Court's suggestion in *Generix* with respect to bioequivalent drugs as a meaningless proposition because, in its opinion, the question of bioequivalence is not one for the courts

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[50] *Supra*, n. 9.

[51] The court below incorrectly states that "the WANS label does not even reveal the chemical makeup of the wax base of the drug." (App. A, *infra*, p. 25a.) Alcon's Exhibit No. 2, the package insert for WANS, (App. K, *infra*, pp. 91a-98a, J.A. 612) fully discloses all of the active and inactive ingredients of WANS, including the "chemical makeup of the wax base" as follows: "The Neocera Base is a blend of Polyethylene Glycol 400, 1540 and 6000. Polysorbate 60 and color additives including FD&C Yellow No. 5 (Tartrazine) in WANS No. 2." Moreover, the package insert for Emerserts (App. M, *infra*, pp. 101a-103a.) also disclosed all of the active and inactive ingredients of Emerserts.

[52] *Generix*, 103 S.Ct. at 1302.

to decide.[53] Under *Alcon,* the clear inference of *Generix* has been now cast in doubt.

CONCLUSION

It is undeniably clear that the opinion of the court below has totally shattered such fragile order as previously existed among the Circuits in the adjudication of "new drug" enforcement actions; and in the process, also has placed the public at unnecessary risk by inhibiting compliance with the FDA's regulations governing the labeling of prescription drugs.

The government's beratement of products not expressly approved by the FDA does not provide a legitimate basis upon which to resolve the questions presented. Recognizing that limitations are to be placed on interpreting the scope of the Act, this Court concluded its opinion in *Bacto-Unidisk, supra,* p. 18 by quoting from its opinion in *62 Cases of Jam* as follows: " 'In our anxiety to effectuate the congressional purpose of protecting the public, we must take care not to extend the scope of the statute beyond the point where Congress indicated it would stop. *62 Cases of Jam* v. *United States,* 340 U.S. 593, 600 (1951).' " From a reading of the Act and its legislative history, it is clear that, in absence of some *genuine* safety or therapeutic

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[53] It is impossible to rationalize the Court of Appeals' holding that it is proper for a court to determine actual safety; *contra, Premo,* § 201(p) *supra;* and what constitutes an "adequate and well-controlled" clinical study, "as a matter of law". *contra, Hynson,* § 505(d), *supra;* but, a court may not even consider expert testimony on bioequivalence. *cf. Generix, supra.*

problem, Congress did not provide that a drug product in the circumstances of WANS is illegal "as a matter of law".

The questions presented are of profound consequence to the consumer as well as the manufacturers of grandfathered drugs. Moreover, the issues involved apply to literally thousands of drugs presently marketed and manufactured by more than three hundred and fifty companies. (App. M, *infra*, 104a-117a.) The rules governing prescription drug labeling for the dissemination of information to the prescribing physician for the public's protection, and the rights and duties of drug manufacturers, deserve and require this Court's further consideration and clarification.

Respectfully submitted,

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APPENDIX

APPENDIX A

UNITED STATES COURT OF APPEALS FOR THE FIRST CIRCUIT

No. 83-1691
83-1693
83-1694
83-1695

UNITED STATES OF AMERICA, *Plaintiff, Appellant,*

v.

ARTICLES OF DRUG CONSISTING OF THE FOLLOWING: 5,906 BOXES, ETC., *Defendants, Appellees.*

No. 83-1692

UNITED STATES OF AMERICA, *Plaintiff, Appellant,*

v.

ALCON LABORATORIES (PUERTO RICO), INC., ET AL., *Defendants, Appellees.*

Appeals from the United States District Court for the District of Puerto Rico

[Hon. Jaime Pieras, Jr., *U.S. District Judge*]

Before
Campbell, *Chief Judge,*
Stewart,* *Associate Justice (Retired),*
and Bownes, *Circuit Judge.*

Randy S. Chartash, Attorney, with whom *J. Patrick Glynn,* Attorney, Office of Consumer Litigation, Civil

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* Of the Supreme Court of the United States, sitting by designation.

Division, Department of Justice, *Richard K. Willard*, Acting Assistant Attorney General, *Daniel Lopez-Romo*, United States Attorney, *Gary H. Montilla*, Assistant United States Attorney, *Thomas Scarlett*, Chief Counsel, *Forrest T. Patterson*, and *Arthur Y. Tsien*, Associate Chief Counsels for Enforcement, Food and Drug Administration, were on brief, for appellant.

Dale B. Hinson, with whom *James D. St. Clair, P.C.*, *James L. Quarles III*, *Hale and Dorr*, *Manuel A. Guzman*, of *McConnell, Valdes, Kelley, Sifre, Griggs & Ruiz-Suria* were on brief, for Alcon Laboratories (Puerto Rico), Inc., et al.

September 28, 1984

STEWART, Justice (Retired):

In the present appeal this court reviews for a second time proceedings instituted by the federal Food and Drug Administration (FDA) against Alcon Laboratories (Alcon) and its drug "WANS" (Webster's Anti-Nausea Supprettes). *See United States* v. *Alcon Laboratories*, 636 F.2d 876 (1st Cir.), *cert. denied*, 451 U.S. 1017 (1981). The issues arise under the Federal Food, Drug and Cosmetics Act of 1938 (the Act), 21 U.S.C. §§ 301-392 (as amended),[1] which provides a statutory structure for the premarketing approval and regulation of drugs that has been described variously as "somewhat complicated," "not straightforward," and even "inconsistent" in its judicial interpretation.[2]

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[1] Pub. L. 75-217, 52 Stat. 1040. The 1938 Act was preceded by the Food and Drugs Act of 1906, 34 Stat. 768. It has been amended on a number of occasions since 1938.

[2] Respectively, *see United States* v. *An Article of Drug (Neo-Terramycin)*, 725 F.2d 976, 978 (5th Cir. 1984); *United States* v. *Articles of Food and Drug (Coli-Trol 80)*, 518 F. 2d 743, 745 n.1 (5th Cir. 1975);

After a seven-day trial in March 1983, a jury answered special interrogatories to the effect that WANS should be exempt from FDA approval because it is currently recognized by experts as safe and effective, and was recognized as safe by experts in 1962. The United States now appeals from that verdict and from the district court's refusal to grant it judgment notwithstanding the verdict (j.n.o.v.).

I. THE STATUTORY STRUCTURE.

The Federal Food, Drug and Cosmetic Act was enacted in 1938. It prohibits the introduction of any "new drug" into interstate commerce unless the FDA has approved the drug as "safe and effective." 21 U.S.C. § 355. The statutory definition of "new drug," however, expressly excludes a drug that is:

> generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, . . . [and if the drug has] been used to a material extent or for a material time under such conditions.

21 U.S.C. § 321(p).

The requirement that a new drug must be "effective" was not part of the 1938 Act. "Effectiveness" was added when Congress amended the Act in 1962 (the 1962 amendments). *See* Pub. L. 87-781, § 102, 76 Stat. 781 (Oct. 10, 1962). A "grandfather clause" in the 1962 amendments specifically exempts from the effectiveness requirements some drugs that were on the market in the United States

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Lemmon Pharmacal Co. v. *Richardson*, 319 F. Supp. 375, 378 (E.D. Pa. 1970). In light of the complexity of this statutory structure, as well as the paucity of precedent in this Circuit, it is perhaps unsurprising that the district court and the parties acted in some confusion with regard to the law.

before the 1962 amendments, if certain conditions are met. *Id.*, § 107(c)(4), *reprinted at* 21 U.S.C. § 321 (note). Because this grandfather clause is central to Alcon's case, we quote it in full:

> In the case of any drug which, on the day immediately preceding the enactment date [i.e., October 9, 1962], (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

This clause thus sets forth *four* conditions that must have been true as of October 1962 for a drug to be exempt from the Act as amended:

> (A) the drug must have been commercially used or sold in this country before 1962;
>
> (B) it must not have been within the definition of a "new drug" in the 1938 Act;
>
> (C) it must not have been covered by an effective new drug application;
> *and*
>
> (D) it must *currently* be "intended solely for use under conditions" prescribed or recommended in its 1962 labeling.

See Alcon Laboratories, supra, 636 F. 2d at 879. With regard to condition (B), the Act's definition of a "new drug" before the 1962 amendments was identical to the present definition quoted above (21 U.S.C. § 321(p), except that "effectiveness" was not included. General recognition by

experts for *safety*, however, has been a requirement for exemption from new drug approval procedures since 1938.

Thus the 1962 grandfather clause simply relieved manufacturers of pre-1962 drugs from having to demonstrate the effectiveness of their drugs, so long as the drugs were generally recognized among experts as safe for certain uses in 1962 and no new conditions of use for the drug are suggested by the manufacturer. As Senator Eastland explained in 1962 "[e]stablished drugs which have never been required to go through new drug procedures will not be affected by the new effectiveness test insofar as their existing claims are concerned." 108 Cong. Rec. 17366 (Aug. 23, 1962); *see USV Pharmaceutical Corp.* v. *Weinberger*, 412 U.S. 655, 664 (1973). But even drugs that were on the market before 1962 must either have been generally recognized as safe in 1962 or be approved today by the FDA.

II. FACTS AND PROCEEDINGS BELOW.

WANS is a rectal suppository drug sold to alleviate the symptoms (but not the underlying causes) of nausea and vomiting. In medical terms it is an "antiemetic," or antivomiting, drug. WANS contains two active ingredients: pyrilamine maleate (an antihistamine) and pentobarbital sodium (a barbituate). WANS also contains "inactive" ingredients in the wax base that is used to bond together the two active ingredients.[3] WANS is manufactured in three different strengths, two for adults and one for children, and has been sold in this country since 1955 (1956 for the childrens' dosage). It was uncontested at trial that

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[3] The WANS label lists only the two active ingredients and the trade name of the wax base ("Neocra"). The wax base makes up 94% of each WANS capsule. The record, but not the WANS label, reveals that the wax base is composed of variations of polyethylene glycol. No other information about the ingredients of the wax base appears in the record.

in the decade from 1970-1980, over 4 million persons used WANS.[4]

Although WANS was clearly a "new drug" in 1955,[5] Alcon never submitted it for FDA approval. Commercial sale of WANS proceeded apparently without incident until 1967. In that year, an FDA official came upon a magazine advertisement for WANS which stated that WANS was "completely safe." Characterizing that description as "untrue and misleading," the official recommended that the FDA take some action against the drug. The FDA subsequently wrote to the manufacturer of WANS[6] and "urged" it to "review" the advertising for WANS. The FDA suggested a number of specific changes in WANS's advertising and promotional literature, and after an exchange of further correspondence all these changes were adopted in WANS's promotional materials.[7] In a subsequent letter, the agency notified the manufacturer that the new advertising materials "appear[ed] to be consistent with [the FDA's] suggestions." The letter expressly

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[4] The parties have filed excerpts from the record in the district court as a Joint Appendix. In the interests of fairness and completeness, however, all 33 volumes of the record have been reviewed by this court. Factual references in this opinion have been drawn from both the Joint Appendix and the record volumes.

[5] As Alcon's expert witness Dr. Crawford stated, WANS "were new drugs to us [practicing physicians] in 1956."

[6] WANS was owned and manufactured by the William A. Webster Co. of Tennessee until the 1970s, when WANS was purchased by Alcon Laboratories. Alcon subsequently moved the WANS manufacturing facility to Puerto Rico; hence the venue of these lawsuits.

[7] These changes included a complete listing of possible side-effects, precautions, and contraindications for WANS; elimination of all recommended uses except those associated with nausea and vomiting; elimination of the claim that WANS was "preferred by physicians and patients of all ages"; and the addition of a statement that WANS should not be administered to children below the age of six months.

noted, however, that the FDA's satisfaction with the new WANS labeling "is not to be in any way construed as constituting official approval either as to the safety or efficacy" of WANS.

In 1975, the FDA began to study the possibility of a relationship between the use of "common medications," such as aspirin, and Reye's Syndrome, a serious childhood disease discovered in the early 1960s and still not fully understood. Because sudden vomiting is a symptom of Reye's Syndrome, one of the types of medication that the FDA focused on was antiemetics such as WANS. In 1976, the FDA assembled an ad hoc panel of experts to study "the role of medications in Reye's Syndrome." This ad hoc committee found that the effectiveness of antiemetics was not demonstrated by any existing studies, and noted that there can be health concerns if antiemetics are used in certain circumstances. The ad hoc committee did not come to any firm conclusions about the safety of antiemetic drugs, but the committee did recommend further study by the FDA. In February 1977, a second FDA committee of experts, the Neurologic Drugs Advisory Committee, noted that "there is a safety issue on [the use of] antiemetics in children." After discussion, however, the Advisory Committee also decided only to request "further information" on the issue from the FDA.

Against this background, the FDA notified Alcon on March 17, 1978, that it believed WANS was being sold unlawfully because it had never been subjected to the FDA's "new drug" approval requirements. The FDA stated that it was "unaware of substantial scientific evidence which demonstrates that WANS is generally recognized as safe and effective for the treatment of nausea and vomiting."[8] In response, Alcon claimed that WANS was

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[8] The FDA apparently sent identical letters to all manufacturers of antiemetic drugs containing the same active ingredients as WANS. Each letter stated that the FDA's advisory committee had reported that chil-

not a "new drug" as defined in the Act and was therefore exempt from the evidentiary requirements relevant to FDA approval.

Consequently, the FDA sought an injunction against the further distribution of WANS under 21 U.S.C. § 332(a) as a "misbranded" and unapproved "new drug." *See* 21 U.S.C. §§ 331(a) & (d), § 352(f)(1). When its motion for a temporary restraining order was denied, the FDA also instituted four seizure actions against WANS under 21 U.S.C. § 334, and large quantities of WANS were seized pending judgment by the court. The injunction and the four seizure actions were consolidated in the district court without objection from the government. They constitute the five cases that have been consolidated for this appeal.

After some discovery, the district court ruled that the seizures were invalid. It enjoined the FDA from further enforcement action and remanded the issues to the FDA for further consideration. On appeal, however, this court ruled that the federal courts lack jurisdiction to enjoin preliminarily FDA seizure actions properly instituted under the Act. *Alcon Laboratories, supra*, 636 F.2d at 881. The court further held that the district court could not interfere with the FDA's administrative enforcement of the Act against WANS unless and until the district court determined the merits of the FDA's position. *Id.* at 883.

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dren treated with WANS-like drugs had "experienced severe and sometimes fatal reactions." This claim was undeniably false. No such report had been made and, in fact, the record indicates that no fatal reactions have ever been associated with WANS. This court referred to this false representation in its prior opinion in this case. 636 F.2d at 879. Alcon understandably made much of this misleading falsehood, once it was discovered. However, despite our concern over the FDA's practice in this case, this court noted in its previous opinion that the law "precludes judicial interference with the FDA's decision to institute enforcement actions, whatever the precise context." *Id.* at 882. The FDA has now admitted its error, and Alcon must defend its position under the statute on the merits, regardless of the FDA's pre-enforcement allegations.

Finally, this court stated that "in view of the fact that the FDA's current position on the 'new drug' status of WANS is already clear," there was no justification for remanding the issue to the FDA; rather the district court should proceed toward trial at which "the FDA carries the burden of proving its position." *Id.* at 888. The case was then remanded "for further proceedings consistent with" the opinion. *Id.* at 889.

Alcon's position on the merits throughout this litigation has been twofold. *First,* Alcon contends that WANS is exempt from the efficacy requirements of the 1962 amendments because it fulfills the conditions of the 1962 grandfather clause. Based on this premise, Alcon further contends that WANS was generally recognized by experts as safe in 1962, and is so recognized today, and that WANS is therefore entirely exempt from the Act's premarket approval system for new drugs because it is not a "new drug" under the pre-1962 statutory definition. *Second,* Alcon contends that even if the grandfather clause does not apply, WANS is now generally recognized by experts as safe *and effective* for the suppression of nausea and vomiting, and therefore does not fall within the definition of "new drug" currently embodied in the Act. Thus it is exempt from approval in any case.

The FDA's position is simply the converse of Alcon's. The FDA contends that WANS does not fall within the 1962 grandfather clause because (1) WANS's current labeling suggests use under conditions different from those suggested in October 1962, and (2) WANS was not generally recognized as safe by qualified experts prior to 1962. As for WANS's current status, the FDA argues that Alcon has not tendered the "substantial evidence" required under the Act to demonstrate a general recognition for effectiveness, and that WANS is also not generally recognized as safe today.

Oddly enough, the FDA consented to submit all these issues to a jury for resolution. We do not believe that such a course was required by this court's previous opinion. While the opinion did note the need for a "judicial determination," 636 F.2d at 883, and referred to the need for a "trial", *id.* at 888, 889, it seems clear that a number of issues could and should have been resolved by the district court judge as a matter of law based on undisputed facts. *See* Fed. R. Civ. P. 50 & 56. For example, the labeling issued for WANS between 1962 and 1983 is undisputed; whether the differences in labeling are significant under the terms of the 1962 grandfather clause is purely a question of law, not fact. Likewise, the government might have sought judgment as a matter of law as to its claim that any "genuine dispute" between qualified experts is enough to preclude a finding of "general recognition" of safety or efficacy. *See* note 22, *infra*. Despite sharp and obvious differences between the FDA and Alcon regarding the proper interpretation of the law governing this case, however, the government never filed a motion for summary judgment.[9]

At trial, the parties stipulated that WANS was not covered by an effective new drug application before the 1962 amendments, and that WANS had been marketed in the United States since 1955. The issues tried were thus limited to differences between WANS's labeling in 1962 and 1983, and the "general recognition among experts" of WANS's safety prior to 1962 and of WANS's safety and effectiveness in 1983. Testimony on these issues was largely a battle of experts. After all the evidence was submitted, the FDA moved for a directed verdict, contending that "it is the government's position [that] there is no factual issue

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[9] In addition, the government submitted proposed special interrogatories for the jury to answer on each of the disputed issues, which did not differ substantially from the interrogatories actually employed by the court.

to be decided by the jury in this case." This motion was denied by the district judge.

Thus the case went to the jury with instructions to answer four questions: was WANS generally recognized as safe by qualified experts prior to the 1962 amendments?; is WANS so recognized as safe today?; is WANS currently intended for use under the same conditions as in 1962?; and is WANS generally recognized as effective today by qualified experts? The first three questions went to applicability of the grandfather clause; the last question was designed to settle WANS's status today if the grandfather clause was found inapplicable. The jury answered each question in the affirmative, and the court accordingly granted judgment for Alcon.[10] The FDA's subsequent j.n.o.v. motion was denied in a written opinion.

III. THE ROLE OF THE JURY IN NEW DRUG CASES.

Immediately prior to submission of this case to the jury, the FDA moved for a directed verdict on the grounds that, in light of the statutory structure and all the evidence adduced by both sides, there was no issue of fact left for the jury to decide. Alcon suggests that to accept this position would be tantamount to usurping the jury's historic, constitutional role.[11] Alcon's argument cannot be accepted as a general proposition. Although the jury's role in deter-

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[10] The district court's judgment did not include an order that Alcon's seized drugs be returned to Alcon. Alcon subsequently filed in the district court what it termed a motion to amend the judgment to effect such a return, and asked this court to dismiss this appeal pending action on that motion. On December 28, 1983, this court ruled that the motion was in effect a request for a post-judgment order and, consequently, that it did not affect this court's appellate jurisdiction. *See* Fed. R. App. 4(a)(4). As far as the record reveals, the district court has not acted on Alcon's motion for return of its property, and the four seizure orders are still in effect.

[11] This position was also alluded to by the district judge in his opinion rejecting the FDA's j.n.o.v. motion.

mining disputed facts cannot be denied in a "new drug" case such as this, neither should a jury be asked to decide issues that are of a legal, not factual nature.

A. Right to Trial by Jury

When injunctive relief and seizure of drugs are sought together in an FDA "new drug" action, it is apparent that the drug manufacturer has a right to have certain issues decided by a jury. An action for an injunction under 21 U.S.C. § 332(a) is, of course, purely equitable in nature, and a jury trial on the injunction alone would not be required under the Seventh Amendment. *United States* v. *Ellis Research Laboratories, Inc.*, 300 F.2d 550, 554 (7th Cir.), *cert. denied*, 370 U.S. 918 (1962); *see United States* v. *Louisiana*, 339 U.S. 699, 706 (1950). But in this case the FDA also brought four actions for seizure and forfeiture against quantities of WANS under 21 U.S.C. § 334. Section 334(b) expressly provides for a trial by jury of "any issue of fact." Moreover, it is well settled that seizure actions, at least on land, are actions at law guaranteed a jury trial under the Seventh Amendment. *C.J. Hendry Co.* v. *Moore*, 318, U.S. 133, 153 (1943). The government did not object to consolidation of the injunction and seizure actions. In any case, the Supreme Court has held that where factual issues are "common" between legal and equitable claims, the right to a jury trial cannot be withheld. *Dairy Queen, Inc.* v. *Wood*, 369 U.S. 469, 479 (1962). Analysis of the instant actions reveals that both might depend ultimately upon determination of the same factual issues: whether WANS was in 1962 and is today generally recognized among qualified experts as safe and (if the grandfather clause does not apply) effective.[12] Thus Alcon had

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[12] The statutory path to this conclusion is intricate but unmistakable. Section 332(a) permits an injunction to issue to restrain violations under § 331; section 331(d) prohibits the introduction into interstate commerce of any article in violation of section 355. Meanwhile, § 334(a)(1) per-

the right to go before a jury on genuinely disputed factual questions.[13]

B. Role of the Jury.

Although the right to a jury trial in a case may be clear, that right is never all-encompassing. "It is, of course, a fundamental of the jury trial . . . that the jury acts, not at large, but under the supervision of a judge." *United States* v. *Taylor*, 464 F.2d 240, 242 (2d Cir. 1972) (citation omitted). Under the Federal Rules of Civil Procedure, a district court judge has both the right and the duty to determine prior to submitting a case to a jury whether there exist material issues of fact that are genuinely disputed. *See* Fed. R. Civ. P. 56(c). "A factual dispute is material if it 'affects the outcome of the litigation,' and genuine if manifested by 'substantial' evidence 'going beyond the allegations [of the party opposing judgment.]' " *Pignons S.A. de Mecanique* v. *Polaroid Corp.*, 657 F.2d 482, 486 (1st Cir. 1981). Thus upon proper pre-trial motion a trial judge

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mits a seizure action to be commenced against any article that may not be introduced into interstate commerce under section 355. Section 355 is therefore common to both types of action. Section 355 declares that no person shall introduce into interstate commerce any "new drug" without prior FDA approval. The definition of "new drug," found in § 321(p) which we have quoted in relevant part at page 2, *supra*, excludes drugs that are "generally recognized among experts" as safe and effective. The 1962 grandfather clause, also quoted *supra* at page 2, includes the identical phrase. Thus "general recognition among experts" can be a factual issue material to the injuctive claims as well as the seizure actions. *See infra*, note 22.

[13] Whether a finding made by a trial judge in a non-jury injunction proceeding that a drug is a "new drug" under section 355 could ever be *res judicata* for purposes of a subsequent seizure action presents an interesting question that we need not decide in this case. *Cf. Neo-Terramycin, supra* note 2, 725 F.2d at 984 ("new drug" finding made by a jury in a seizure action would be "*res judicata* in a subsequent injunction action").

must carefully sift the evidence submitted by all parties to determine whether disputes are factual (as opposed to legal) and "genuine," and then further review and interpret relevant statutes, to see if any genuine factual dispute is "material" to the merits of the case.

Even after evidence has been presented to the jury, a judge must carefully review all the evidence before submitting the case for the jury's consideration, and determine whether each party has adduced evidence sufficient to warrant a verdict in its favor. If the court finds that such is not the case, it may grant a directed verdict without asking the jury for findings. *See* Fed. R. Civ. P. 50(a); *Brady* v. *Southern Railway Co.*, 320 U.S. 476, 479-80 (1943). Finally, even after a jury has rendered a verdict, if the trial court decides after careful reconsideration that the evidence was insufficient to submit the case to the jury after all, it has the power to grant a judgment *non obstante veredicto* and reverse the jury's verdict. Fed. R. Civ. P. 50(b). The exercise of the judicial perogative to terminate a case must be painstaking. Nevertheless, whether there exist factual questions sufficiently disputed to warrant a verdict for either side is an issue of law, not fact, and its determination is quintessentially the function of the trial judge, not the jury.

Because of the constitutional status of the right to trial by jury, exercise of the judicial power to terminate a case is also subject to a stringent standard of review. Thus a directed verdict can be ordered only when,

> viewing the evidence in the light most favorable to [the party opposing the motion, the court] find[s] that, "without weighing the credibility of the witnesses or otherwise considering the weight of the evidence, there is only one verdict reasonable men could reach."

Trinidad v. *Pan American World Airways, Inc.*, 575 F.2d 983, 984 (1st Cir. 1978), *quoting Harrington* v. *United*

States, 504 F.2d 1306, 1311 (1st Cir. 1974). The standard for reviewing a judgment n.o.v. is similar if not identical: "The motion is properly granted only when, as a matter of law, no conclusion but one can be drawn." *Rios* v. *Empresas Lineas Maritimas Argentinas*, 575 F.2d 986, 990 (1st Cir. 1978); *accord*, *Robinson* v. *Watts Detective Agency*, 685 F.2d 729, 733 (1st Cir. 1982), *cert. denied*, 459 U.S. 1105 & 1204 (1983). Nevertheless it should be clear that, while special deference is due the verdict of a civil jury, "nothing in the Seventh Amendment removes the appellate court's duty to correct errors of law." *Ballwanz* v. *Isthmanian Lines, Inc.*, 319 F.2d 457, 460 (4th Cir. 1963), *cert. denied*, 376 U.S. 970 (1964). Thus, in a "new drug" case as in any other, the trial court as well as this court has an obligation to render judgment as a matter of law when it is clear from the evidence that such is required.

IV. MERITS ON APPEAL.

Upon careful consideration of the Act, its purposes and legislative history, and the evidence submitted at trial by both parties, we have concluded that the FDA's motion for a directed verdict should have been granted in this case. As a matter of law the evidence was insufficient to ask the jury to consider whether WANS is or was "generally recognized among experts" as safe or effective, because certain evidentiary requirements under the Act simply were not fulfilled. This conclusion applies to Alcon's showing under the 1962 grandfather clause as well as under the current Act.

A. The 1962 Grandfather Clause.

If WANS meets the conditions of the grandfather clause, *see supra*, pp. 2-3, then it is exempt from the current effectiveness requirements. We therefore consider this issue first. We note at the outset that, as an exemption to a comprehensive regulatory statute concerned with public

safety, the grandfather clause is to be strictly construed, and Alcon bears the burden of poof as to each condition. *See United States* v. *Allan Drug Corp.*, 357 F.2d 713, 718 (10th Cir.), *cert. denied*, 385 U.S. 899 (1966); *United States* v. *An Article of Drug (Bentex Ulcerine)*, 469 F.2d 875, 878 (5th Cir. 1972), *cert. denied*, 412 U.S. 938 (1978).

1. Labeling

The grandfather clause provides that a pre-1962 drug will not be exempt from the 1962 amendments unless it is currently "intended solely for use under conditions prescribed, recommended, or suggested in labeling" of the drug prior to 1962. "Labeling" is broadly defined in the Act (21 U.S.C. § 321(m)):

> The term "labeling" means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.

Prior to trial the parties stipulated as to what documents constituted "labeling" for WANS prior to 1962 and at the time of trial. Thus all the facts material to the labeling issue were undisputed,[14] and the only issue to be resolved was one of law for the court, applying the statutory lan-

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[14] Alcon now suggests that certain file cards distributed to physicians to promote WANS in 1961 do not constitute "labeling" for purposes of the grandfather clause. Even if Alcon had not stipulated to the contrary, we would find otherwise. The Supreme Court has ruled that labeling under this same statutory provision includes any literature that "supplements or explains" a drug, including "advertising or descriptive matter"—"[n]o physical attachment one to the other is necessary." *Kordel* v. *United States*, 335 U.S. 345, 350 (1948). In light of the normal rule that "safety legislation is to be liberally construed to effect the congressional purpose," *Whirlpool Corp.* v. *Marshall*, 445 U.S. 1, 13 (1980), Alcon's argument on this point is frivolous.

guage "intended solely for use under conditions." This issue simply was not one of fact for the jury to decide.[15]

Pre-1962 labels suggest a number of uses for WANS other than suppression of nausea and vomiting. These other uses were eliminated from WANS labels in 1967 after the FDA took issue with them. The FDA contends that this change alone requires judgment against Alcon on this issue; the FDA's position is that pre-1962 and current labeling must be "exactly the same" for the grandfather clause to apply. *See United States* v. *1,048,000 Capsules (Afrodex)*, 347 F. Supp. 768, 770 (S.D. Tex. 1972), *aff'd*, 494 F.2d 1158 (5th Cir. 1974); *Allan Drug Corp., supra*, 357 F.2d at 719 (labeling must "contain[] the same representations concerning its use").

Alcon, however, cites legislative history of the grandfather clause to the effect that the 1962 amendments were intended to address only "new uses" of existing drugs. *See, e.g.* S. Rep. No. 1744, Part 1, 87th Cong., 2d Sess. 17 (July 19, 1962) ("Any such new use would have to be submitted" for FDA approval); S. Rep. No. 1744, Part 2, 87th Cong., 2d Sess. 8 (Aug. 21, 1962) ("existing claims will be exempt"); 108 Cong. Rec. 17,366 (Aug. 23, 1962) (remarks of Sen. Eastland) (same). Since WANS was recommended for the suppression of nausea and vomiting in 1962 and is so recommended today, Alcon asserts that the labeling condition of the grandfather clause is satisfied.

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[15] Alcon's witness Dr. Crawford, an experienced pediatrician who has prescribed WANS for his patients since 1956, testified that in his opinion WANS is currently intended for use under the same conditions found in the 1962 labeling. Because this is a legal issue and not a medical question, Dr. Crawford was not qualified to offer this opinion, and his testimony on the subject was irrelevant. The same applies to the FDA's misguided attempts to have its own medical experts address the question. For similar reasons, the correspondence between the FDA and WANS's manufacturer indicating the FDA's satisfaction with WANS's labeling in 1967 is irrelevant to this issue. The WANS labeling speaks for itself.

Alcon dropped the other suggested uses for WANS in 1967 after the FDA evinced some concern about the safety of those uses. An argument can be made that such voluntary relabeling to eliminate questionable uses of an unapproved drug is to be encouraged, and that the literal language of the grandfather clause does not require that such corrective relabeling operate to transform old drugs into "new" ones requiring FDA approval. *See Allan Drug Corp., supra,* 357 F.2d at 721 (Seth, J., dissenting) ("It would seem that the purpose of the Act is to encourage label corrections rather than to discourage them.") We need not decide this issue in the present case, however, because it is clear from the stipulated labeling that the "conditions" for use of WANS suggested specifically in connection with vomiting and nausea have changed significantly since 1962.

It must be noted that the operative term in the statutory language appears to be "conditions," not "use." We read the language to mean that even if particular *uses* of a drug are the same, a change in the suggested *conditions* for its use will suffice to remove the drug from the protection of the grandfather clause. Current WANS labeling states that "WANS is indicated in the symptomatic treatment of nausea and vomiting," without apparent qualification as to cause. Yet the 1962 WANS labeling listed eleven specific types of, or causes of, nausea and vomiting under "indications." Nothing in the record indicates that these eleven causes are the only possible causes of nausea and vomiting, however, and trial testimony revealed that a number of other conditions can cause vomiting. Thus the current WANS labeling suggests that the drug be used for conditions not listed in the 1962 labeling.

Furthermore, in 1962 WANS labeling stated that WANS was "Preferred by . . . Patients of all ages" and that "Children . . . of all ages tolerate [WANS] exceptionally well". In stark contrast, current WANS labeling states,

apparently in bold print, "Do not use in infants below the age of 6 months." It further indicates that WANS is "not recommended for treatment of uncomplicated vomiting in children and . . . should be limited to prolonged vomiting of known etiology [i.e., cause]." The labeling goes on to discuss the "suspicion" of a link between drugs like WANS and Reye's Syndrome, the same concern that led the FDA to bring this action. Thus it appears that the suggested "conditions" for use of WANS in children have changed dramatically since 1962. We do not view this labeling change as simply a minor correction of possibly erroneous claims. Instead, it indicates that new information about the health effects of WANS has become available since 1962, information that Alcon apparently considers reliable enough to include on its labels. This new information, and WANS's changed labeling, indicate that the "existing claims" made for WANS with regard to nausea and vomiting in 1962 are no longer accurate. The general purpose of the Act to protect the public's health and safety would be ill-served if such new labeling information had no effect on an unapproved drug's regulatory status. The new conditions now suggested for use of WANS in the treatment of nausea and vomiting are sufficient to take WANS out of the grandfather clause and place it squarely within the requirements of the Act as amended.

2. Lack of Scientific Testing.

Even if WANS met the labeling condition of the grandfather clause, the clause would still be inapplicable as a matter of law, because Alcon has produced absolutely no scientific testing evidence of WANS's safety in 1962. We believe it clear as a matter of statutory interpretation that at least some scientific drug testing for safety must have been performed prior to 1962 to fulfill the general recognition requirement of the grandfather clause.

Section 505(b) of the 1938 Act required that drug manufacturers submit "as part of the [new drug] application (1) full *reports of investigations which have been made* to show whether or not such drug is safe for use." Pub. L. 75-717, § 505(b) (codified as subsequently amended at 21 U.S.C. § 355(b)) (emphasis supplied). Section 505(d) went on to provide that the new drug application "shall" be disapproved if "the investigations [required by § 505(b)] . . . do not include *adequate tests by all methods reasonably applicable* to show whether or not such drug is safe for use" (emphasis supplied). Explaining § 505(b), the 1938 House Report stated that "new drugs [are] to be adequately tested," and referred to "laboratory and clinical tests" and "the manufacturer's tests." H.R. Rep. No. 2139, Part 1, 75th Cong., 3rd Sess. 9 (April 14, 1938). In addition, the contemporary administrative interpretation of the provision reflects the requirement of "scientific studies." *See* Sellers & Grundstein, *Administrative Procedure and Practice in the Department of Agriculture under the Food, Drug, and Cosmetic Act of 1938*, at 92 (1940), *reprinted in* H. Toulmin, Jr., *The Law of Food, Drugs and Cosmetics* § 411 (1st ed. 1942). In this contemporary monograph written by an attorney and a staff member in the Department of Agriculture (the department responsible for the FDA in 1940), the authors state with regard to § 505(b) that "[t]he Administration insists upon a certain amount of empirical, clinical testing on humans before it will regard a new drug as safe." *Id.* at 93. General publication of such studies does not seem to have been required, but the requirement of some valid testing is clear: "In rendering a decision that a drug is safe, . . . the Administration will accept any valid tests, regardless of source, . . . so long as they can be shown to have scientific validity." *Id.*[16]

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[16] Thus the FDA's argument that a pre-1962 general recognition of safety must be based upon *published* investigations meeting *current* standards for scientific validity is not well-taken. Pre-1962 recognition need

In addition to the plain language of sections 505(b) and (d) of the 1938 Act, great deference is due the contemporary interpretation given to the Act by those originally charged with its administration. *Zenith Radio Corp.* v. *United States,* 437 U.S. 443, 450 (1978).

Alcon argues that the evidentiary standards for new drug applications under § 505 are not applicable in a case where the very claim at issue is that no new drug application is required because WANS in 1962 was not a "new drug" as defined in § 201(p) of the 1938 Act. This argument is foreclosed, however, by the Supreme Court's reasoning in *Weinberger* v. *Hynson, Wescott & Dunning, Inc.,* 412 U.S. 609, 628-32 (1973). In *Hynson,* a drug manufacturer argued that the "substantial evidence" standard for proof of effectiveness found in § 505 of the Act was not applicable to the requirement for demonstrating the general recognition of effectiveness referred to in the "new drug" definition of § 201(p). Thus *Hynson* involved the precise question that is at issue here: should the requirements for new drug applications be read into the definitional requirements for "new drugs" under the Act? The Court rejected the position which Alcon advocates (412 U.S. at 631)[17]:

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meet only the standards for scientific validity as they were understood at that time, and general publication evidently was not required. The Supreme Court's decision in *Weinberger* v. *Hynson, Westcott & Dunning, Inc.,* 412 U.S. 609 (1973) is not to the contrary. That opinion set forth only the requirements for effectiveness under the 1962 amendments. As has been noted, the requirements for demonstrating efficacy and those for safety under the Act "are governed by different sections of the law, different legislative histories and different regulations." *Hess & Clark, Division of Rhodia, Inc.* v. *Food & Drug Admin.,* 495 F.2d 975, 985 (D.C. Cir. 1974); *see also E.R. Squibb & Sons* v. *Weinberger,* 483 F.2d 1382, 1385 (3rd Cir. 1973).

[17] Alcon is correct that the *Hynson* case specifically involved only the evidentiary requirements for demonstrating effectiveness under the 1962

> [W]e cannot construe § 201(p) to deprive FDA of jurisdiction over a drug which, if subject to FDA regulation, could not be marketed because it had not passed the "substantial evidence" test. To do so "would be to impute to Congress a purpose to paralyze with one hand what it sought to promote with the other." *Clark* v. *Uebersee Finanz-Korp.*, 332 U.S. 480, 489 [1947].

In a companion case to *Hynson*, the Court succintly explained its holding: "the reach of scientific inquiry [for effectiveness] under both § 505(d) and § 201(p) is precisely the same." *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 653 (1973). Likewise, "the reach of scientific inquiry" required for safety under §§ 505(d) and 201(p) should also be "precisely the same," and the safety of a pre-1962 drug must be demonstrated by some sort of contemporaneous, valid scientific tests for the grandfather clause to be fulfilled.[18] It would be anomalous to hold that Alcon could now avoid the full weight of the burden to demonstrate safety that it would have had to satisfy in 1955 (when WANS clearly was a "new drug") simply because Alcon marketed WANS for seven years without seeking FDA approval.

It is undisputed that there is no evidence of any scientific testing of WANS for safety prior to 1962. Thus, as a matter of law, Alcon's evidence was insufficient to support

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amendments, and not those for safety. *See* note 16, *supra*. This fact, however, provides no justification for ignoring the Court's reasoning with regard to statutory construction of the Act and the specific relationship between sections 201(p) and 505.

[18] We recognize that Alcon depends on application of the "general recognition" language of the 1962 grandfather clause, while we have interpreted that same language in § 201(p) of the 1938 Act. There is no logical reason to believe that the identical language was intended by Congress to have different meanings in those two contexts, however, and we conclude that their meaning is the same.

a finding of "general recognition of safety" prior to 1962. *See United States* v. *41 Cases, More or Less,* 420 F.2d 1126, 1130 (5th Cir. 1970). The FDA's motion for a directed verdict on the grandfather clause questions therefore should have been granted.

B. The Current Status of WANS.

Because the 1962 grandfather clause does not apply to WANS as a matter of law, WANS must meet the requirements of the Act as currently in force. Alcon contends that even under the current Act, WANS is exempt from FDA approval because it is now "generally recognized among experts . . . as safe and effective." 21 U.S.C. § 321(p). It is true that the jury found affirmatively for Alcon on those issues. But, again, the record requires the conclusion that the factual questions of "general recognition" should not have been submitted to the jury in the first place, because Alcon failed to introduce the type of "substantial evidence" of effectiveness required by the Act as a matter of law.

Under the *Hynson* decision, *supra,* the evidentiary standards for effectiveness required for a new drug application under 21 U.S.C. § 355(d) must also be applied to any drug for which "general recognition of effectiveness among experts" is claimed under § 321(p). Section 355(d)(5) requires that an application be rejected if the FDA finds a "lack of substantial evidence that the drug will have the effect it purports or is represented to have." Substantial evidence is defined in the same subsection as "evidence consisting of *adequate and well-controlled investigations,* including clinical investigations, [conducted] by experts. . . ." (emphasis supplied). WANS's claimed effectiveness must be supported with evidence of this kind for it to obtain exemption from new drug approval requirements today.

Alcon concedes that no investigations of any kind have ever been conducted to test WANS's efficacy. But at trial it successfully introduced three studies conducted in 1968 and 1969 using a drug called Emeserts.[19] Emeserts is an antiemetic like WANS which contains the same amounts of the same active ingredients found in WANS. There is no evidence in the record concerning the "inactive" ingredients in either drug. *See* note 3, *supra*. Alcon's theory is that WANS and Emeserts are, in effect, the same drug, and that the Emeserts studies were "adequate and well-controlled investigations" within the meaning of § 355(d). Thus Alcon argues that the Emeserts studies may be considered as evidence that demonstrates WANS's effectiveness.

The testimony of one of Alcon's experts, Dr. Kalman, was directed largely to this issue. Dr. Kalman had never personally examined WANS or Emeserts by chemical or other scientific means; he based his testimony simply on his reading of the drug products' labels (including their lists of ingredients) and some other, unspecified "information furnished to [him] by Alcon." He then offered his theoretical opinion that the clinical effects of Emeserts and WANS would be "identical or nearly so," although the drugs "may not be identical in terms of" their inactive ingredients.

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[19] The FDA contends that admission of these studies violated Fed. R. Evid. 803 (18). That rule bars the introduction of "learned treatises" upon which an expert has relied (although the text may be read to the jury), in order to prevent "misunderstanding and misapplication" of principles contained in the treatises by the jury "without expert assistance and supervision." *Id.* (Notes of the Advisory Committee). At trial, however, counsel for the FDA refused to stipulate that the three studies even existed, stating at the time it could not stipulate to their existence while maintaining an objection to their relevance. Such a position is erroneous. In light of the FDA's refusal to stipulate that the studies existed, we do not find the district court's limited admission of the studies to prove that fact to be in error.

There are a number of reasons why this testimony is insufficient as a matter of law to support application of the Emeserts test results to an evaluation of WANS. *First*, there is precedent for rejecting an expert's "theoretical evaluation" of a drug. *United States* v. *7 Cartons, More or Less (Ferro-lac)*, 293 F. Supp. 660, 666 (S.D. Ill. 1968), *aff'd in part and vacated in part*, 424 F.2d 1364 (7th Cir. 1970). We doubt that a review of a drug product's label and unrevealed "information" supplied by the interested drug company is sufficient foundation on which to base an expert opinion as to the clinical effects of two drugs. This is especially true where, as here, the WANS label does not even reveal the chemical makeup of the wax base of the drug. *See* note 3, *supra*. *Second*, Dr. Kalman did not testify that Emeserts and WANS are bioequivalent; he qualified his testimony by stating that the drugs were identical "or nearly so." It is well recognized that so-called inactive ingredients "may affect the rate at which the active ingredient is delivered." *United States* v. *Generix Drug Corp.*, 460 U.S. 453, 455 (1983). Indeed, there was unrebutted trial testimony in this case to the effect that WANS's wax base may contribute to the "erratic absorption" of its active ingredients, which in turn can result in health dangers due to an oversupply of the active ingredients in the bloodstream. In the absence of any expert testimony specifically addressing the inactive ingredients in the two drugs, bioequivalence of Emeserts and WANS was, as a matter of law, not demonstrated.[20]

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[20] Even if Emeserts and WANS had been shown to be bioequivalent, it is still an open question "whether two demonstrably bioequivalent products, containing the same active ingredients but different [inactive ingredients] might under some circumstances to be the same 'drug'" for purposes of the Act. *Generix*, *supra*, 453 U.S. at 461. We are especially reluctant to conclude that evidence concerning inactive ingredients is unnecessary under the Act in light of the historical fact that it was an allegedly inactive ingredient in "Elixer of Sulphanilamide" that caused fatalities in 1937 and led directly to enactment of the 1938 Act in its

The deciding factor on this issue, however, is that even if the Emeserts studies could be substituted as evidence of WANS's effectiveness, the testimony of Alcon's own expert leads to the unavoidable conclusion that those studies were not the sort of "adequate and well-controlled investigations" required by § 355(d). Alcon's witness Dr. Brown, who was qualified by the district court as "an expert in statistics and clinical trials," testified that the Emeserts studies were comparable to "other papers [published] during that era [i.e., the late 1960s]," but that they "did, for the most part, fail to use some of the methods that most recently . . . have come to be regarded as more important in the [design] of clinical [investigations]."[21] Because Alcon has chosen not to submit a new drug application for WANS in the past, however, it is subject to the effectiveness standards employed by experts today, not 15 years ago. In light of the testimony of Alcon's own expert

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present form. *See* 5 *A Legislative History of the Federal Food, Drug, and Cosmetic Act and Its Amendments* 885-897 (U.S. Dept. HEW 1979) (report to the Senate from the Secretary of Agriculture on "Deaths Dues To Elixer Sulphanilamide") (Nov. 25, 1937). *Cf. Generix, supra*, 453 U.S. at 459 (the term "drug" in the Act means "entire drug products, complete with active and inactive ingredients").

The Second Circuit has suggested that it is improper for the district court to engage in the scientific inquiry required to determine whether two drugs are "theraputic equivalents." *Premo Pharmaceutical Laboratories, Inc.* v. *United States*, 629 F.2d 795, 803 (2d Cir. 1980). The court noted that "the entire statutory scheme envisages that the FDA will perform the difficult task of investigation and scientific evaluation usually required" under the statute. *Id.* We do not decide in this case whether or not the issue of bioequivalence can ever be one for the court to decide.

[21] Dr. Brown also noted that one Emeserts test method has "long been discredited," and he conceded that a number of design features recommended in his own 1977 textbook for inclusion in the design of biomedical studies were not included in the design of the Emeserts studies. Dr. Brown's testimony on this issue was corroborated by that of the FDA's expert Dr. Tolman, who testified extensively as to why the Emeserts studies were not "adequate and well-controlled."

that the Emeserts studies did not meet present-day standards for "adequate and well-controlled investigations," and considering all the other evidence on this issue in the record, it is clear as a matter of law that Alcon failed to produce the types of studies required to demonstrate "substantial evidence" of effectiveness.

For all these reasons, the Emeserts studies could not and should not have been applied to WANS in this case. As a matter of law, therefore, Alcon failed to meet the "substantial evidence" requirement of § 355(d). Thus it was premature and unnecessary to submit to the jury any question of WANS's "general recognition among experts" for effectiveness; Alcon's preliminary evidence required by the statute on this issue was legally insufficient to create an issue for the jury. Consequently, the FDA's motion for a directed verdict on the question of current recognition of effectiveness should also have been granted.

V. CONCLUSION.

A careful and thorough review of all the evidence submitted at trial, evaluated in light of the language, purposes and history of the Act, yields certain unmistakable conclusions. *First*, no pre-1962 studies concerning WANS's safety were submitted at trial, and the stipulated labeling materials for WANS demonstrate a significant change in the conditions for WANS's use since 1962. *Second*, the scientific studies submitted at trial to demonstrate WANS's general recognition of effectiveness fail to meet the minimal statutory requirements for "substantial evidence." These conclusions, which are clear as a matter of law based on undisputed facts, pretermit the need for a factual inquiry into the "general recognition among experts" of WANS's safety and effectiveness.[22] Based upon the fore-

[22] Because the statutory prerequisites were not fulfilled as a matter of law in this case, we do not reach the argument advanced by the FDA that a "genuine conflict" between the testimony of expert witnesses in a new

going, we conclude that "as a matter of law, no other conclusion but one can be drawn" from all the evidence presented at trial. *Austin* v. *Unarco Industries, Inc.*, 705 F.2d 1, 17 n.9 (1st Cir. 1983). That conclusion is that WANS is subject to the current Act as amended in 1962, that it is not now generally recognized among qualified experts as safe and effective, and that it is a new drug subject to the requirements of 21 U.S.C. § 355. Accordingly, the judgments in the five cases before us are reversed, and the district court is directed to enter judgments consistent with this opinion.

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drug trial is sufficient to mandate judgment for the FDA on the issue of "general recognition." Interpretation of the "general recognition among experts" standard has troubled trial and appellate courts for some time, because "the Act . . . nowhere defines what constitutes 'general recognition' among experts." *Hynson, supra*, 412 U.S. at 629. Although the question of general expert recognition may clearly be a factual one at some level, *see, e.g., Neo-Terramycin, supra*, 725 F.2d at 985; *United States* v. *An Article of Food*, 622 F.2d 768, 771 (5th Cir. 1980); *United States* v. *Articles of Drug (Quick-O-Ver)*, 274 F. Supp. 443, 448 n.7 (D.Md. 1967), not every conflict in expert testimony is sufficient to create a question for the jury. *See, e.g., Premo, supra*, 629 F.2d at 803 (no general recognition when there is a "severe conflict" in expert testimony); *United States* v. *X-Otag Plus Tablets*, 441 F. Supp. 105, 114 (D. Colo. 1977) (same when there is a "sharp difference of opinion"), *aff'd in revelant part*, 602 F.2d 1387 (10th Cir. 1979); *United States* v. *Article of Drug (Mykocert)*, 345 F. Supp. 571, 575 (N.D. Ill. 1972) (same when there is "more than a 'mere' conflict" in expert testimony). The congressional purpose of removing the complex medical and scientific aspects of drug disputes from the courts to the expert province of the FDA would be frustrated if any and every divergence in expert opinion could serve to send a new drug case to the jury. It is by now clear that unanimity among experts is not required to demonstrate "general" recognition. *Coli-Trol, supra*, 518 F.2d at 746; *Quick-O-Ver, supra*, 274 F. Supp. at 448 n.7. Nevertheless, we agree that "the cited cases . . . require a discriminating analysis of the [expert testimony] submitted by the parties to determine whether there really is a triable issue as to general recognition." *Lemmon Pharmacal, supra*, 319 F. Supp. at 378.

APPENDIX B

UNITED STATES COURT OF APPEALS
FOR THE FIRST CIRCUIT

No. 83-1691
83-1693
83-1694
83-1695

UNITED STATES OF AMERICA, *Plaintiff, Appellant,*

v.

ARTICLES OF DRUG CONSISTING OF THE FOLLOWING:
5,906 BOXES, ETC., *Defendants, Appellees.*

No. 83-1692

UNITED STATES OF AMERICA, *Plaintiff, Appellant,*

v.

ALCON LABORATORIES (PUERTO RICO), INC., ET AL.,
Defendants, Appellees.

JUDGMENT

Entered: September 28, 1984

These causes came to be heard on appeals from the United States District Court for the District of Puerto Rico, and were argued by counsel.

Upon consideration whereof, It is now here ordered, adjudged and decreed as follows: The judgment of the District Court is reversed and these five cases are remanded to the District Court to enter judgment consistent with the opinion filed this date.

By the Court:
Francis P. Scigliano
Clerk.

[cc: Messrs. Chartash, Guzman & Hinson]

APPENDIX C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF PUERTO RICO

Civil No. 78-2378 (JP)
UNITED STATES OF AMERICA, *Plaintiff*

vs.

ALCON LABORATORIES (PUERTO RICO), INC., a corporation, and EDGAR H. SCHOLLMAIER and LEE HANSEN, individuals, *Defendants*

Civil No: 78-1830;
80-0243;
80-2112;
82-0055

UNITED STATES OF AMERICA, *Plaintiff*

vs.

ARTICLES OF DRUG . . . "WANS, etc., *Defendant*

ORDER

At the conclusion of a jury trial lasting more than a week, the jury rendered its verdict on special interrogatories in favor of the defendants. Following entry of judgment for defendants, plaintiff filed its Motion for Judgment Notwithstanding the Verdict in the above consolidated cases pursuant to Rule 50(b) F.R. Civ. Proc.

In such motion plaintiff contends that the drugs in question, WANS, are "new drugs" under the provisions of the Federal Food, Drug and Cosmetic Act (the Act), 21 U.S.C. 321(p). Defendants contend that such drugs are "generally recognized as safe and effective" under the same section of the Act; and alternatively, that said drugs are "grand-

fathered" under the provisions of Section 107(c)(4) of the Drug Amendments of 1962, P.L. 87-781.

The jury verdict which plaintiff seeks by its motion to set aside is as follows:

"VERDICT

"We, the jury, unanimously answer the interrogatories submitted by the Court as follows:

1. Do you find from a preponderance of the evidence that before October 10, 1962 the WANS products were generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as being safe for use under the conditions then prescribed, recommended or suggested in their labeling?

Yes X
No _____

2. Do you find from a preponderance of the evidence that the WANS products are generally recognized among experts qualified by scientific training and experience to evaluate the safety of drugs, as being safe for use under the conditions prescribed, recommended or suggested in their labeling at the present time?

Yes X
No _____

3. Do you find from a preponderance of the evidence that the WANS products are presently intended solely for use under the same conditions prescribed, recommended or suggested in their labeling as was in use on October 9, 1962?

Yes X
No _____

4. Do you find from a preponderance of the evidence that the WANS products are generally recognized, among experts qualified by scientific training and experience to evaluate the effectiveness of drugs, as effective for use under the conditions prescribed, recommended or suggested in their labeling at the present time?

Yes X
No ____"

The legal effect of the jury's findings was in support of both contentions made by defendants.

Plaintiff's arguments in support of its motion center upon the following issues:

1. The recent Supreme Court ruling in *United States v. Generix Drug Corp.*, No. 81-1222 precludes the above quoted jury verdict.

2. The WANS products have not been and cannot be generally recognized as safe and effective for the following reasons:

(a) The existence of a genuine dispute among experts precludes general recognition of safety or efficacy; and

(b) There are no published reports establishing the safety of WANS; and

(c) There are no published reports establishing the effectiveness of WANS; and

(d) There was no testimony by qualified experts that WANS were generally recognized as safe in 1962.

3. The WANS products cannot qualify for the "grandfather" exemption because the conditions of use as set forth in the labeling thereof have changed since 1962.

In considering the government's motion to set aside the jury's verdict the criteria under which to review such motion is well settled in this Circuit. Under such standards, the Court is to first review the evidence as well as all reasonable inferences deducible therefrom in the light most favorable to the prevailing party. *Robinson v. Watts Detective Agency*, 685 F.2d 729, 732-733 (1st Cir. 1982); *Engine Specialties, Inc. v. Bombardier Ltd.*, 605 F.2d 1, 3 (1st Cir. 1979), cert. denied, 446 U.S. 983 (1980). "The motion is properly granted only when, as a matter of law, no conclusion but one can be drawn", *Robinson, supra*, at 733, such conclusion having been made without evaluating the credibility of witnesses or the weight of the evidence at trial. *Hubbard v. Faros Fisheries, Inc.*, 626 F.2d 196, 199 (1st Cir. 1980). *Austin v. Unarco Industries*, slip op. March 30, 1983, at p. 40. 703 F.2d —— (1st Cir. 1983). Mere disagreement with the jury's verdict will not support the motion, *Keeler v. Hewitt*, 697 F.2d 8, 11 (1st Cir. 1982) and the trial judge is not to act as thirteenth juror. *Coffran v. Hitchcock Clinic, Inc.*, 683 F.2d 5, 6 (1st Cir. 1982).

The Court has carefully reviewed all of the evidence produced by the parties to determine whether such evidence and the reasonable inferences deducible therefrom substantially and separately support each of the jury's answers to the special interrogatories.

Having done so, the Court finds plaintiff's arguments to be without merit for the following reasons:

1. The Supreme Court's ruling in *Generix, supra*, does not necessarily preclude the jury findings herein. The *Generix* decision involved the definition of a "drug" under the Act. It is noted that the Supreme Court was careful to point out that:

> "We thus do not reach the issue of whether two demonstrably bioequivalent products containing the

same active ingredients but different excipients, might under some circumstances be the same 'drug'."

It may reasonably be inferred from the evidence and jury findings herein that the jury found that the WANS products were "demonstrably bioequivalent" to the product evaluated in the published studies upon which defendants rely. Defendants produced three published studies reporting the results of clinical investigations conducted with a drug product known as Emeserts. In this connection defendants also provided evidence with respect to the similarity between the two products and their therapeutic equivalence. Such evidence, specifically pertaining to the two products in question, was not controverted.

2. The Court of Appeals for this circuit remanded this case for trial in the course of which, among other things, it stated the following:

> "The Supreme Court has described the 'new drug' and 'grandfather clause' issues as 'the kinds of issues peculiarly suited to initial determination by the FDA.' Nevertheless, contrary to the Court's suggestion it has not been 'commonplace' for the courts to await an appropriate administrative declaration in enforcement proceedings; lower courts continue to hear and decide the 'new drug' status of drugs challenged by the FDA in seizure and injunction actions.
>
> * * * * *
>
> Had the trial set for May 1979 been held, WANS' status would long since have been laid to rest. In deciding the case, the FDA's expertise would have been available to the court, in that to sustain its burden the agency would have had to present expert evidence establishing its claims regarding WANS. We therefore conclude that the district court erred in remanding the case to the FDA.

> The orders of the district court are vacated and the case is remanded for further proceedings consistent with this opinion." (citations omitted) *United States v. Alcon Laboratories,* 636 F.2d 876 (1st Cir. 1981).

It is therefore clear that the Court of Appeals contemplated an adjudication by trial of the "new drug" and "grandfather" issues involved. Moreover, it is self-evident that "dispute among experts" would be the inevitable consequence of a trial on the merits as ordered by the Court of Appeals. Plaintiff's argument that the mere existence of a dispute among experts entitles it to judgment is not persuasive since the result of such a proposition would effectively deny at the outset defendant's right to trial on the merits.

The jury could also have believed that there was no "genuine" dispute among the experts. The credentials of defendants' expert witnesses were unimpeachable. The evidence offered by plaintiff was not so overwhelming as to preclude disbelief. The record clearly supports the inference that the jury believed that there was no "genuine" dispute among the experts.

3. Plaintiff contends that general recognition of safety prior to October 10, 1962 must be predicated on adequate data published in the scientific literature. Defendants produced correspondence with the Food and Drug Administration which at the very least, tacitly recognized the safety of WANS. Defendants also produced evidence to the effect that there has never been any basis for questioning the safety of WANS and that said products were generally recognized by qualified experts as safe. In this connection it is noted that defendants produced the medical reviewing officer from the Food and Drug Administration who first originated documents questioning the safety of WANS. From such testimony one can only conclude that the jury did not believe such allegations were supported by the facts

disclosed at trial. The published studies upon which defendants rely were also shown to provide confirmation of general recognition of safety. There was, therefore, sufficient evidence upon which the jury found that the WANS products were, before October 10, 1962, and are at the present time, generally recognized by qualified experts as being safe.

4. Plaintiff's contentions with respect to the studies relied upon by defendants are also without merit. There was sufficient evidence to support the inference that the jury believed that the studies in question were "adequate and well controlled" and, therefore, provided "substantial evidence" of efficacy. There was also a sufficient basis upon which the jury could have found that WANS and Emeserts were sufficiently similar so as to have the same therapeutic effect. Such evidence, as offered by defendants with respect to the composition and similarity of the two products, was not controverted by plaintiff. Plaintiff's argument that there are no published studies equating the WANS and Emeserts products is not persuasive. Defendants' expert pharmacologist testified that the dosage strengths, active ingredients and inactive ingredients of the two products were so closely related as to justify treating the two products as being the same product.

5. Plaintiff also argues that defendants' expert witnesses were not qualified to testify with respect to the matters in issue. Three of defendants' experts were professors associated with the School of Medicine at Stanford University and had previously been consultant to the government; and the fourth was a practicing pediatrician who had served as Chairman of the State Formulary Committee of Kentucky and also held various teaching positions. The jury could easily have found that all of defendants' expert witnesses were eminently well qualified insofar as such expertise relates to their respective testimony in this case.

6. Plaintiff's arguments with respect to a change in the conditions of use in the labeling of WANS subsequent to 1962 was expressly found by the jury to the contrary. There was ample evidence in support of such finding. Defendants' stipulation to the effect that any printed matter pertaining to WANS is, in the broadest sense, labeling, does not operate to negate the more precise definition pertaining to the labeled "conditions of use".

Having reviewed the evidence as well as all reasonable inferences properly deducible therefrom in the light most favorable to defendants, the Court cannot say that such facts and inferences point so strongly and overwhelmingly in favor of the government that reasonable and fair-minded jurors could not have arrived at a contrary verdict.

Accordingly, the government's Motion for Judgment Notwithstanding the Verdict is DENIED.

IT IS SO ORDERED.

In San Juan, Puerto Rico, this 15 day of June, 1983.

/s/ JAIME PIERAS
Jaime Pieras, Jr.
U. S. District Judge

APPENDIX D

STATUTES AND AMENDMENTS

The Federal Food, Drug, and Cosmetic Act of 1938

[PUBLIC—No. 717—75TH CONGRESS]
[21 U.S.C. 321(g)]

[CHAPTER 675—3D SESSION]

[S. 5]

AN ACT

* * * * * * * * *

1. Sec. 201(g), the Act of 1938 [21 U.S.C. 321(g)]

(g) The term "drug" means (1) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (2) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (3) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (4) articles intended for use as a component of any article specified in clause (1), (2), or (3); but does not include devices or their components, parts, or accessories.

* * * * * * * * *

2. Sec. 201(p), the Act of 1938 [21 U.S.C. 321(p)]

(p) The term "new drug" means—

(1) Any drug the composition of which is such that such drug is not generally recognized, among experts

qualified by scientific training and experience to evaluate the safety of drugs, as safe for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug the composition of which is such that such drug, as a result of investigations to determine its safety for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

* * * * * * * * *

Drug Amendments of 1962

3. PUBLIC LAW 87-781; 76 STAT. 780, Sec. 107(c)(4)

* * * * * * * * *

(4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

* * * * * * * * *

4. Sec. 201(p) the Act, as amended. [21 U.S.C. 321(p)]

* * * * * * * * *

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the condition prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to the enactment of this Act [June 25, 1938] it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

* * * * * * * * *

5. Sec. 505(d), the Act, as amended [21 U.S.C. 355(d)] provides in pertinent part:

* * * As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including

clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

APPENDIX E

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF PUERTO RICO

Nos. 78-2378, 78-1830, 80-243

(Filed April 9, 1980)

UNITED STATES OF AMERICA,

v.

ALCON LABORATORIES (PUERTO RICO), INC., *et al.*

Before Juan M. Perez Gimenez, *Judge*

OPINION AND ORDER

Through an order issued by this Court on February 27, 1980, this matter was remanded to the Food and Drug Administration for further proceedings "with instructions to defer regulatory action against the WANS preparations involved in the matter against defendants, based upon the alleged 'new drug' status of WANS until F.D.A. holds a hearing pursuant to 5 U.S.C. 554, and thereafter makes an administrative determination of the new drug status of WANS in conformity with the enforcement priorities enunciated in F.D.A.'s Compliance Policy Guide 7132c.08".

The present matter consists of three consolidated actions presenting similar issues.[1] Involved herein are a series of petitions for seizure and condemnation by the United

[1] Two of the three actions, Civil No. 78-1830 and 80-0243, are seizure actions. The other, Civil No. 78-2378, is an injunctive action, whereby the Food and Drug Administration sought to enjoin the defendants from introducing WANS into interstate commerce without an approved new drug application, a petition for temporary retraining [*sic*] order was denied on November 29, 1978.

States of America under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301, et seq., for seizure and condemnation of WANS, and any other article of drug consisting of pyrilamine maleate and pentobarbital sodium, manufactured by Alcon Laboratories (Puerto Rico), Inc., Humacao, Puerto Rico, alleging that the aforesaid articles are held illegally within the jurisdiction of the Court since they are new drugs which may not be introduced or delivered for introduction into interstate commerce.

The Government has alleged that the specific articles of drug are "new drugs" within the meaning of Section 201 (p) of the Federal Food, Drug and Cosmetic Act (the Act), 21 U.S.C. 321(p), and that the articles are misbranded under Section 502(f)(1) of the Act, 21 U.S.C. 352 (f)(1), in view that their labeling fails to bear adequate directions for use.

The term "new drug" is defined in 21 U.S.C. 321(p) as follows:

> "(1) Any drug . . . the composition of which is such that such drug is not generally recognized among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof. . . .
> "(2) Any drug . . . the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions has become so recognized, but which has not, otherwise, than in such investigations been used to a material extent or for a material time under such conditions."

On the other side, Alcon denies that the seized articles are "new drugs", and advances three additional arguments in support of its position, to wit: (1) that the drugs

are entitled to the protection under the 1962 "grandfather" clause; (2) that regulatory action is premature because there is no significant new information which questions the safety or effectiveness of the drugs within the meaning of the F.D.A.'s Compliance Policy Guide 7132c.08 (21 C.F.R. 10.85(e));[2] (3) that the initiation of enforcement actions against WANS based upon the marketing of WANS without an approved N.D.A. (New Drug Application) not only violates F.D.A.'s own rules, policies and regulations (21 C.F.R. 10.85(e)), but that it is also not in accordance with the law, 5 U.S.C. 706(2)(A).[3]

In the instant case the Government instituted these actions based on information obtained by the Food and Drug Administration which relates to reports of adverse reactions in children who were treated for nausea and vomit-

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[2] 21 C.F.R. 10.85(e), (f), provides: "(e) An advisory opinion represents the formal position of the Food and Drug Administration on the matter involved, and except as provided in paragraph (f) of this section obligates the agency to follow it until it is amended or revoked. The Commissioner shall not recommend legal action against any person or product with respect to any action taken in conformity with an advisory opinion which has not been amended or revoked.

"(f) In unusual situations involving an immediate and significant danger to health, the Commissioner may take appropriate civil enforcement action contrary to an advisory opinion issued pursuant to this section prior to amending or revoking such advisory opinion as provided in paragraph (g) of this section. Appropriate amendment or revocation of the advisory opinion involved shall be expedited."

[3] 5 U.S.C. 706(2)(A) provides: "To the extent necessary to decision and when presented, the reviewing court shall decide all relevant questions of law, interpret constitutional and statutory provisions and determine the meaning or applicability of the terms of an agency action. The reviewing court shall:

(2) hold unlawful and set aside agency action, findings, and conclusions found to be

(A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law."

ing with drugs containing pyrilamine maleate and pertobarbital [*sic*] sodium.

Alcon contends that the information is not new information within the meaning of the Compliance Policy Guide. It is averred that the seven adverse reactions in question occurred between 1970 and 1974 (as per deposition of Dr. James F. Schwartz on February 13, 1979), that the attending physicians, contrary to what they say, did not consider these reactions significant enough at the time in view of the failure to report them to the Food and Drug Administration (as per Dr. Pruitts' deposition, p. 40), and that the regulatory letter was issued more than 14 months later from the period of time mentioned before.

The validity of the "new information" has been further challenged by Alcon. It has been alleged that each adverse reaction was associated with an "overdose" and that each patient was dehydrated; that dehydration itself produces similar symptoms.[4] Additionally, there is the fact that in most of the cases cited the patient was receiving or had recently received other drug therapy.

Furthermore, there are discrepancies between Dr. Pruitt's Drug Experience Reports as submitted to F.D.A. and Dr. Schwartz' notes from the hospital charts of the seven patients as to the amount, dosage, strength, and brand name of the antihistamine barbiturate drug administered, and as to the prior or concurrent drug therapy.

Certainly, in these actions complex technical determinations are involved concerning the "new drug" issue. The definition of "new drug" as used in Section 201(p), involves a determination of technical and scientific questions

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[4] Dr. Pruitt, who collected the information on the adverse reactions cited by F.D.A., indicated that lack of drug therapy in cases of pernicious vomiting can cause dehydration which in turn can result in the same adverse reactions said to be associated with the antihistamine barbiturate products.

by experts. *Ciba Corp.* v. *Weinberger,* 412 U.S. 640, 643 (1973). Moreover, the determination of whether a drug is generally recognized as safe and effective within the meaning of Section 201(p)(1) necessarily implicates complex chemical and pharmacological considerations. *Weinberger* v. *Bentex Pharmaceuticals,* 412 U.S. 645 (1973). When as in the present action there are conflicts arising from the medical data, an order to remand would be the most adequate determination.

In the case of *Weinberger* v. *Bentex Pharmaceuticals, supra,* the United States Supreme Court ruled that the evaluation of conflicting reports as to the reputation of drugs among experts in the field is not a matter well left to a court without chemical or medical background, and further established that threshold questions within the peculiar expertise of an administrative agency are appropriately routed to the agency, while the court stays its hand. *Weinberger. Bentex, supra,* at 653-654.

The present actions have been instituted without a formal administrative determination of the "new drug" status of WANS, the issue first being tendered to the district court.

The Act does not create a dual system of control, one administrative and one judicial, for it is the agency's primary jurisdiction to determine the status of drugs under the Act. Thus, issues presented herein may be more effectively evaluated at the administrative than at the judicial level, and a remand would promote both administrative and judicial economy. The question whether the drug is to be recognized as "safe and effective" or was "grandfathered in" are the kinds of issues peculiarly suited to initial determination by the Food and Drug Administration. *Weinberger* v. *Bentex, supra,* at 653.

Given the present state of the evidence on record, a remand would be the most proper action to be taken. *Weinberger* v. *Bentex, supra,* at 654.

It is not within the jurisdiction of this Court to determine whether the drug in issue is or is not a new drug. Such decision corresponds, and is to be made by the Food and Drug Administration, the Agency entrusted by Congress with the necessary expertise to make a responsible determination. A remand to the F.D.A. would be the most appropriate action to be taken in view of the characteristics of the case as reflected through information generated by the discovery had so far in the cases and which appears on the record.

There is evidence in the record which establishes that the WANS proportions have been used under medical supervision for approximately twenty five years. In conjunction with this fact we have to consider that the alleged "new information" poses a series of conflicts when examined with other evidence on record. Both factors are determinant for any conclusion by the Court as to whether regulatory action against WANS violates C.P.G.[5]

Since no final determination has been made with respect to WANS, in order to proceed or initiate regulatory action against the product, there must be significant new information which questions the safety of the drug. At this stage, and in the light of the "new information" the Court cannot make a well-informed decision and is unable to determine the direct relationship establishing that WANS is an unsafe product. As a corollary to this, the Court, given the conflicts which appear from the evidence, is in no position to ascertain whether the F.D.A.'s enforcement actions against WANS are consistent with its Compliance Policy Guide.[6]

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[5] The Food and Drug Administration's Compliance Policy Guide 7132c.08 constitutes an advisory opinion/guideline enunciating F.D.A.'s "new drug" enforcement properties. 21 C.F.R. 10.85, 10.90.

[6] It has been established that enforcement actions premised upon the Government's contravention of the Compliance Policy Guide cannot stand. *N.L.R.B.* v. *Welcome American Fertilizer Co.*, 443 F.2d 19 (9 Cir. 1971).

This Court finds that issues pending in these actions revolve and are dependent on the "new drug" status of the WANS, this in turn being a matter to be resolved at the agency level. *C.B.A. Corp.* v. *Weinberger, supra.*

Wherefore, in view of the foregoing, the Court hereby ORDERS that consolidated cases Civil Nos 78-2378, 78-1830 and 80-0243, be remanded to the Food and Drug Administration to hold a formal administrative hearing pursuant to 5 U.S.C. 554 on the issue as to whether WANS is a "new drug" in conformity with the enforcement priorities enunciated in F.D.A.'s Compliance Policy Guide 7132c.08.

The Court will retain jurisdiction over these actions for purposes of (1) determining whether any verifiable and genuinely significant new information comes to light which questions the safety and efficacy of a WANS preparation so as to justify enforcement action against such preparations out of the sequence provided by the Agency's Compliance Policy Guide 7132c.08, and; (2) resolving any issues remaining following the issuance of a final administrative order after a formal administrative hearing on the "new drug" status of WANS in conformity with the enforcement priorities established in Compliance Policy Guid [*sic*] 7132c.08.

IT IS SO ORDERED.

San Juan, Puerto Rico, April 8, 1980.

/s/ JUAN M. PEREZ-GIMENEZ
Juan M. Perez-Gimenez
U. S. District Judge

APPENDIX F

UNITED STATES OF AMERICA, *Appellant,*

v.

ALCON LABORATORIES, etc., et al., *Defendants, Appellees.*

Nos. 80-1188, 80-1357.

United States Court of Appeals,
First Circuit.

Argued Oct. 10, 1980.

Decided Feb. 24, 1981.

The United States appealed from orders of the United States District Court for the District of Puerto Rico, Juan M. Perez-Gimenez, J., in two seizure actions and suit for injunctive relief instituted by Food and Drug Administration against pharmaceutical company and one of its drugs. The Court of Appeals, Levin H. Campbell, Circuit Judge, held that: (1) District Court's interlocutory order that FDA defer further regulatory action against company and its product was one granting an injunction, and therefore, was appealable; (2) this injunction exceeded District Court's authority; (3) so much of District Court's orders as purported to leave FDA's prior seizures of drug "without effect" was appealable as a collateral order; (4) District Court erred in dissolving administrative seizures of drug without first addressing merits of seizure proceedings initiated by FDA, including, as a part thereof, agency's contention that drug was a "new drug;" (5) District Court's remand order was an appealable collateral order; and (6) District Court erred in remanding case to FDA.

Vacated and remanded.

* * * * * * * * *

Before COFFIN, Chief Judge, PELL* and CAMPBELL, Circuit Judges.

LEVIN H. CAMPBELL, Circuit Judge.

The United States appeals from orders of the District Court for the District of Puerto Rico in two seizure actions and a suit for injunctive relief instituted by the Food and Drug Administration (FDA) against Alcon Laboratories, Inc. (Alcon) and one of its products pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-92 (1976).

Alcon manufactures and markets in suppository dosage a prescription antiemetic drug called "WANS." The drug contains pyrilamine maleate (an antihistamine) and pentobarbital sodium (a barbituate) and comes in three dosage strengths, WANS No. 1, WANS No. 2 and WANS Children. WANS has been used under medical supervision for approximately 25 years, and did not become an object of FDA concern until 1978. To understand what then transpired, it is first useful to review parts of the Federal Food, Drug, and Cosmetic Act.

Section 505 of the Act forbids the introduction into interstate commerce of any "new drug" unless the FDA has approved a New Drug Application (NDA) for the product. 21 U.S.C. § 355. Section 201 (p) defines a "new drug" as

> "(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, . . . or

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* Of the Seventh Circuit, sitting by designation.

> (2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions."

21 U.S.C. § 321(p). Obtaining approval of an NDA requires the submission of extensive scientific data and can be slow and expensive, *see* Note, New Drug Approval: *Lannett*, The Drug Lag and the NDA System, 11 Rut.-Cam. L.J. 231, 231-34; 248-53 (1980), but Congress imposed these burdens in furtherance of a compelling purpose: "to protect the public against danger to human life arising from use of unsafe and ineffective drugs by assuring that before any drug is marketed it will have been carefully reviewed by FDA experts." *Premo Pharmaceutical Laboratories, Inc. v. United States*, 629 F.2d 795, 802 (2d Cir. 1980).

A product may be marketable without prior FDA approval for any of three reasons. First, a drug is not a "new drug" if "generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof"; if this "expert consensus is founded upon 'substantial evidence' "; *and* if the drug has "been used to a material extent or for a material time under such conditions." 21 U.S.C. § 321(p); *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 631-32, 93 S.Ct. 2469, 2484, 37 L.Ed.2d 207 (1973); *Premo Pharmaceutical, supra*, 629 F.2d at 801-02. Second, under a "grandfather" clause inserted in the 1938 Act, drugs which prior to June 25, 1938 (the effective date of the

Act) were "subject to the Food and Drugs Act of June 30, 1906" and have since undergone no change in composition, labeling or recommendations for use are exempt from Section 505's premarketing approval requirements. 21 U.S.C. § 321(p)(1). And third, another grandfather clause in the Act, added in 1962, relieves from premarketing approval any drug which prior to October 10, 1962 (the effective date of the 1962 amendments) "was commercially used or sold in the United States," was generally recognized as safe by qualified experts, was not covered by an effective new drug application and has undergone no change in composition or labeling. Comment to 21 U.S.C. § 321.

Where the FDA believes that a drug is a "new drug" and is being marketed without approval of an NDA, it is empowered to institute seizure and injunction actions in federal district court to remedy the alleged violation of the Act. 21 U.S.C. § 332, 334. The agency may also seek criminal sanctions. 21 U.S.C. § 333.

On March 17, 1978, the FDA sent Alcon a regulatory letter informing it of a report received from the agency's Neurological Drugs Advisory Committee "that children aged 6 months to seven years who were treated for nausea and vomiting with drugs containing pyrilamine maleate and pentobarbital, experienced severe and sometimes fatal reactions." The Committee had concluded, the letter went on, "that there is no evidence of safety and efficacy for drugs containing pyrilamine maleate with or without a barbituate in the treatment of nausea and vomiting." Based on the Committee's report, "and because [the FDA was] unaware of substantial scientific evidence which demonstrates that a combination of these ingredients is generally recognized as safe and effective for the treatment of nausea and vomiting," the FDA advised Alcon that it considered Alcon's marketing of WANS to be in violation of the "new drug" provision of the Federal Food, Drug,

and Cosmetic Act, 21 U.S.C. § 355. The letter stated that under FDA regulatory policy as formulated in Compliance Policy Guide 7132c.08, *see infra*, WANS had become subject to immediate regulatory action outside the agency's ordinary enforcement priorities "because of new information concerning the safety and efficacy of these drugs." Alcon was told to reply within ten days, and was warned that failure to discontinue marketing WANS would expose the company to seizure and injunction actions.

Alcon responded on April 3, 1978. It claimed that WANS was not a "new drug," objected to the FDA's departure from the ordinary sequence of its enforcement priorities on the basis of an "unsubstantiated, conclusionary indictment of the safety" of the active ingredients in WANS, and requested that it be allowed to "identify and review the data and information upon which the Agency relies, and to make a formal submission to the Agency. . . ." The company also offered to revise the labeling of WANS consistent with the findings of its review. Subsequent to this letter, Alcon, on its own initiative, sent the FDA proposed new labeling for WANS and information supporting the safety and efficacy of the drug. Various company officials met with agency officials on July 10 and 18, 1978 to discuss WANS.

The FDA reviewed the materials provided by Alcon and in a letter of August 4, 1978 reaffirmed its position upon the "new drug" status of WANS: "the data submitted . . . contains no adequate scientific data to support the safety and efficacy of the Wans products." Though the proposed relabeling was felt to be "an improvement," it could not substitute for "scientific evidence to establish that a fixed combination of pyrilamine maleate and pentobarbital sodium is either safe or effective for the treatment of nausea and vomiting." The letter made no reference to Compliance Policy Guide 7132c.08 or to the enforcement priority scheme delineated therein.

Alcon continued to manufacture WANS and on September 21, 1978 the FDA instituted a seizure action in federal district court alleging that the drug was a "new drug" being marketed in violation of Section 505 of the Act, 21 U.S.C. § 355. By court order, a large quantity of WANS suppositories (approximately 453,900) was seized. In its responsive pleadings in the seizure action, Alcon admitted that no approval of a new drug application was in effect for WANS or was being sought. The company nevertheless denied that WANS was being marketed in violation of section 505. Alcon argued that WANS is not subject to the "new drug" requirements of the Act because "it is generally recognized as safe for use under the conditions prescribed, recommended or suggested in its labeling, and it is exempted from the 'efficacy' requirements of the Federal Food, Drug and Cosmetic Act" by the 1962 grandfather clause discussed *supra*. In addition, Alcon contended that the FDA was acting in violation of its pertinent Compliance Policy Guide.

Despite seizure of the suppositories, Alcon continued to manufacture and distribute WANS, thus prompting the FDA, on November 28, 1978, to institute a further action, this time seeking a temporary restraining order, a preliminary injunction and a permanent injunction against continued marketing of WANS without FDA approval. On the next day, November 29, the district court denied the FDA's request for a temporary restraining order, and consolidated the injunctive suit with the earlier seizure action. On December 19, 1978, the district court gave the parties 90 days to complete discovery in the consolidated proceeding set a trial date of May 7, 1979.

On March 21, 1979, however, Alcon moved the district court to remand to the FDA,

> "with instructions to defer regulatory action against the WANS preparations involved in this matter or

against defendants based upon the alleged 'new drug' status of WANS until FDA makes an administrative determination of the new drug status of WANS in conformity with the enforcement priorities enunciated in FDA's Compliance Policy Guide 7132c.08 and the requirements of the Administrative Procedure Act, or unless verifiable and genuinely significant and new information surfaces which questions the safety or efficacy of a WANS preparation so as to justify taking regulatory action against such preparation out of the sequence provided by the Agency's Compliance Policy Guide 7132c.08."

No further action was taken in the case until January 28, 1980. On that date the FDA instituted a second seizure against WANS. Large quantities of the drug were again confiscated. A month later, on February 27, 1980, the district court consolidated the latest seizure action with the pending actions, and ordered the entire case to be,

"remanded to the Food and Drug Administration (FDA) with instructions to defer regulatory action against the WANS preparations involved in this matter or against defendants based upon the alleged 'new drug' status of WANS until FDA holds a hearing pursuant to 5 U.S.C. § 554 and thereafter makes an administrative determination of the new drug status of WANS in conformity with the enforcement priorities enunciated in FDA's Compliance Policy Guide 7132c 08.

"Accordingly, it is FURTHER ORDERED

"That prior seizures ordered by the Court are left without effect.

"However, jurisdiction will be retained whether new, verifiable and genuinely significant information comes to light which questions the safety or efficacy

of a WANS preparation so as to justify enforcement action against such preparation out of the sequence provided by the Agency's Compliance Policy Guide 7132c.08."

On April 8, 1980, the district court issued an Opinion and Order explaining and reiterating this order. We treat the two orders, which are the same but for their date of issuance, as a single order.

The United States filed separate appeals from the orders of February 27 and April 8, and these have been consolidated. The United States also moved for, and we have granted, a stay pending appeal with respect to the district court's order enjoining future seizures, and ordering the return of quantities of the drug already seized.

The United States presently attacks three aspects of the district court's order: (1) its instruction that the FDA "defer regulatory action against the WANS preparation . . . or against defendants" pending further administrative proceedings; (2) its decision to leave prior seizures of WANS "without effect"; and (3) its remand of the case to the agency. We consider these issues in turn; and in connection with each we also address this court's appellate jurisdiction.[1]

The Order to "Defer" Regulatory Action

Our jurisdiction to review the district court's interlocutory order that the FDA defer further regulatory action against WANS and Alcon depends on whether the order is appealable as one granting an injunction, *see* 28 U.S.C. § 1292(a)(1), or is simply, as Alcon contends, an exercise

[1] Alcon has moved for summary dismissal of the government appeals, asserting lack of appellate jurisdiction. We advised that we would consider the motion when deciding the merits.

of the court's discretion in controlling a case before it. Looking to the order's "substantial effect," *see United States v. Cities Service Co.*, 410 F.2d 662, 663 n.1 (1st Cir. 1969); *Hotel & Restaurant Employees and Bartenders International Union v. Del Valle*, 328 F.2d 885, 886 (1st Cir.), *cert. denied*, 379 U.S. 879, 85 S.Ct. 146, 13 L.Ed.2d 86 (1964), we think it was an injunction, hence appealable under section 1292(a)(1). The order has the effect of forbidding the FDA from exercising in any forum its statutory power both to proceed against WANS and its producer and to seize the article pending condemnation. Absence of the word "enjoin" does nothing to mitigate the blanket severity of the decree. Whether regulatory action against a possibly unsafe or ineffective drug must be "deferred" or is "enjoined" is a matter of semantics. In either case, the agency is denied the ability to take summary steps to protect those to whom the drug will be distributed in the interim.

This injunction exceeded the district court's authority. To prevent this sort of eroding of the agency's protective powers, the Supreme Court in *Ewing v. Mytinger & Casselberry, Inc.*, 339 U.S. 594, 70 S.Ct. 870, 94 L.Ed. 1088 (1950), held that district courts lack jurisdiction to enjoin multiple seizure actions instituted by the FDA under the Act. The rule of *Ewing* has been consistently and strictly observed, *see Southeastern Minerals, Inc. v. Harris*, 622 F.2d 758 (5th Cir. 1980); *Pharmadyne Laboratories, Inc. v. Kennedy*, 596 F.2d 568 (3d Cir. 1979); *Parke, Davis & Co. v. Califano*, 564 F.2d 1200 (6th Cir. 1977), *cert. denied*, 435 U.S. 942, 98 S.Ct. 1522, 55 L.Ed.2d 539 (1978;) *Natick Paperboard Corp. v. Weinberger*, 498 F.2d 125 (1st Cir. 1974), *cert. denied*, 429 U.S. 819, 97 S.Ct. 65, 50 L.Ed.2d 80 (1976), and controls the present case. We see no distinction between this case and *Ewing* merely because the latter involved multiple seizures for alleged misbranding, which may be instituted only when there is probable cause

to believe that the article is dangerous or that the misbranding may be fraudulent or misleading. Risks to consumers may be present in new drug cases, and the same section of the Act is involved. *See* 21 U.S.C. § 334(a)(1). The Supreme Court's decision in *Ewing* precludes judicial interference with the FDA's decision to institute enforcement actions, whatever the precise context. *Compare Southeastern Minerals, supra,* 622 F.2d at 763-64 *with Parke, Davis & Co., supra,* 564 F.2d at 1205 *and Natick Paperboard, supra,* 498 F.2d at 126-27. Alcon's argument that such a rule exposes a manufacturer to potentially devastating hardship and loss was disposed of in *Ewing. See* 339 U.S. at 604-05, 70 S.Ct. 875-76 (Jackson, J., dissenting). The considerations from which the *Ewing* holding emerged dictate that it be applied and that the district court's order, insofar as it bars initiation of further FDA enforcement actions, be vacated:

> "The purpose of the multiple seizure provision is plain. It is to arrest the distribution of an article that is dangerous, or whose labeling is fraudulent or misleading, pending a determination of the issue of adulteration or misbranding. The public therefore has a stake in the jurisdictional issue before us. If the District Court can step in, stay the institution of seizures, and bring the administrative regulation to a halt until it hears the case, the public will be denied the speedy protection which Congress provided by multiple seizures.
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> "The means which Congress provided to protect consumers against the injurious consequences of protracted proceedings would then be seriously impaired. Congress weighed the potential injury to the public from misbranded articles against the injury to the purveyor of the article from a temporary interference with its distribution and decided in favor of the

> speedy, preventive device of multiple seizures. We would impair or destroy the effectiveness of that device if we sanctioned the interference which a grant of jurisdiction to the District Court would entail. Multiple seizures are the means of protection afforded the public. Consolidation of all the libel suits so that one trial may be had is the relief afforded the distributors of the articles."

339 U.S. at 601-02, 70 S.Ct. at 873-74 (footnotes omitted). *See also Premo Pharmaceutical, supra*, 629 F.2d at 801; *Natick Paperboard, supra*, 498 F.2d at 127.

The Dissolution of Prior Seizures

We agree with the United States that so much of the district court's order as purports to leave the FDA's former seizures "without effect" is appealable as a collateral order. *See Cohen v. Beneficial Industrial Loan Corp.*, 337 U.S. 541, 69 S.Ct. 1221, 93 L.Ed. 1528 (1949), discussed *infra* in connection with the remand order. The present situation is like that in *Swift & Co. Packers v. Compania Colombiana Del Caribe*, 339 U.S. 684, 70 S.Ct. 861, 94 L.Ed. 1206 (1950), where the *Cohen* rule was held to apply. The Supreme Court there stated,

> "Appellate review of the order dissolving the attachment at a later date would be an empty rite after the vessel had been released and the restoration of the attachment only theoretically possible. Under these circumstances the provision for appeals only from final decisions in 28 U.S.C. § 1291 should not be construed so as to deny effective review of a claim fairly severable from the context of a larger litigious process."

339 U.S. at 689, 70 S.Ct. at 865 (citations omitted). The same can be said as to the futility of later appellate review

of this order requiring, it would seem, immediate release of the seized suppositories. We therefore turn to the merits of the present appeal.

It is the government's contention that the district court "ha[d] no authority simply to give back the seized property without determining . . . whether or not the Act [was] violated." The Act provides that before trial the court shall "allow any party to a condemnation proceeding . . . to obtain a representative sample of the article seized" and that after condemnation the court has discretion to order the goods sold or destroyed, 21 U.S.C. § 334(c), (d), but otherwise is silent upon the release of seized goods prior to a decision upon the FDA's claims. Rule E(5)(c) of the Supplemental Rules for Certain Admiralty and Maritime Claims, which were intended to inform seizure procedure under the Act, *see* 21 U.S.C. § 334(b), states that seized property held by the marshal

> "may be released forthwith upon his acceptance and approval of a stipulation, bond, or other security, signed by the party on whose behalf the property is detained or his attorney and expressly authorizing such release, if all costs and charges of the court and its officers shall have first been paid. Otherwise no property in the custody of the marshal or other officer of the court shall be released without an order of the court; but such order may be entered as of course by the clerk, upon the giving of approved security as provided by law and these rules, or upon the dismissal or discontinuance of the action; but the marshal shall not deliver any property so released until the costs and charges of the officers of the court shall first have been paid."

Alcon contends that this portion of Rule E(5) implies some general grant of authority to a court to order the release of seized property. However, the purpose and focus

of Rule E(5) is merely to describe the circumstances under which seized property may be released prior to a court's determination of the merits; thus it provides for release of property if a plaintiff consents, or when "approved security as provided by law and these rules" is tendered. Neither circumstance exists here (and, indeed, in a new drug case, where the purpose of the seizure is to remove a possibly risky drug from public use, it is hard to see how the mere putting up of security would be a proper basis for release). In any event, we see little in Rule E(5) by way of a general grant of authority permitting courts to countermand administratively instituted seizures without first adjudicating the merits of the agency's claim. If the seizure is plainly frivolous, the court can act rapidly and achieve justice in that manner, but its action should ordinarily follow, not precede, an adjudication. We have found only two cases that bear on the question. One holds, and the other suggests, that articles seized in an FDA enforcement action may not be released by the court prior to a judicial determination of whether they violate the Act. *See In re United States*, 140 F.2d 19 (5th Cir. 1943); *United States v. 893 One-Gallon Cans . . . Brown's Inhalant*, 45 F.Supp. 467 (D.Del.1942).

We conclude that the district court erred in dissolving the administrative seizures of WANS without first addressing the merits of the seizure proceedings initiated by the FDA, including, as part thereof, the agency's contention that WANS is a "new drug." We therefore vacate this portion of the district court's order. The district court believed that allowing "the continued retention of the material seized would be an abuse of judicial discretion" in light of its findings that WANS "has been used for years" and that "the information which prompted the F.D.A. to initiate these actions was not only contradictory, but also insufficient to allow a causal relation." These preliminary and necessarily tentative and incomplete findings cannot

serve as a substitute for determination on the merits. It has been said that in pursuing a seizure action, the FDA must first allege sufficient facts to state a claim and must then prove its claim by a preponderance of the evidence. *See United States v. 47 Bottles . . . Jenasol RJ Formula '60'* ", 320 F.2d 564, 569-71 (3d Cir.), *cert. denied*, 375 U.S. 953, 84 S.Ct. 444, 11 L.Ed.2d 313 (1963); *United States v. 4 Cases . . . Slim-Mint Chewing Gum*, 300 F.2d 144, 148-50 (7th Cir. 1962). A decision by a district court as to whether the FDA has met those burdens would be the proper means for adjudicating the validity of the FDA's enforcement efforts; a seizure should only be dissolved thereafter, in event of the government's failure to do so.

The Remand to the FDA

Remand of a case for further proceedings is ordinarily not appealable in that it is not a "final decision" from which appeals may be taken under 28 U.S.C. § 1291. *See Pauls v. Secretary*, 457 F.2d 294 (1st Cir. 1972). The government, however, argues that the district court's order in this case is appealable under section 1291 as a collateral order within the meaning of *Cohen v. Beneficial Industrial Loan Corp., supra*, 337 U.S. 541, 69 S.Ct. 1221, 93 L.Ed. 1528.

In *Cohen*, the Supreme Court held that a district court's refusal to order the plaintiff in a stockholders' derivative suit to post security for costs as required by a state statute was immediately appealable because it fell in "that small class" of decisions "which finally determine claims of right separable from, and collateral to, rights asserted in the action, too important to be denied review and too independent of the cause itself to require that appellate consideration be deferred until the whole case is adjudicated." 337 U.S. at 546, 69 S.Ct. at 1225. We have inter-

preted the Court's formulation in *Cohen* to require that appealability be predicated on four characteristics:

> "The order must involve: (1) an issue essentially unrelated to the merits of the main dispute, capable of review without disrupting the main trial; (2) a complete resolution of the issue, not one that is 'unfinished' or 'inconclusive'; (3) a right incapable of vindication on appeal from final judgment; and (4) an important and unsettled question of controlling law, not merely a question of the proper exercise of the trial court's discretion."

United States v. Sorren, 605 F.2d 1211, 1213 (1st Cir. 1979), *quoted in In re Continental Investment Corp.*, 637 F.2d 1, at 4 (1st Cir. 1980). The requisites may be summarized as separability, finality, urgency, and importance. *In re Continental Investment Corp., supra*, slip op. at 6. *Cf. Grinnell Corp. v. Hackett*, 519 F.2d 595, 596 (1st Cir.), *cert. denied sub nom. Chamber of Commerce v. United Steelworkers*, 423 U.S. 1033, 96 S.Ct. 566, 46 L.Ed.2d 407 (1975) (arguing that "urgency" necessarily subsumes "finality"). *See generally Firestone Tire & Rubber Co. v. Risjord*, 449 U.S. ——, ——-——, 101 S.Ct. 669, 672-76, 66 L.Ed.2d 571 (1981). We find each characteristic to be present here and so hold that the order is appealable.

First, the remand order raises issues that are entirely separable from the ultimate question to be decided by this litigation, the "new drug" status of WANS. In remanding, the court ordered the FDA to hold "a hearing pursuant to 5 U.S.C. § 554 and thereafter make[] an administrative determination of the new drug status [of] WANS in conformity with the enforcement priorities enunciated in FDA's Compliance Policy Guide 7132c.08." The decree thus implicates the power of the agency to summarily initiate enforcement proceedings under the Act and its own regulations. It also puts at issue the manner in which

FDA enforcement actions ought to proceed. These issues are independent of the merits of the underlying claim against WANS. *See Lopez v. Secretary*, 512 F.2d 1155 (1st Cir. 1975) (allowing appeal from remand requiring Secretary of HEW to show claimant had a "realistic opportunity" of being hired for available positions); *Gueory v. Hampton*, 510 F.2d 1222, 1224-25 (D.C.Cir. 1975) (allowing appeal from remand that required Civil Service Commission to show how conduct for which employee was dismissed had diminished the efficiency of the service); *Gold v. Weinberger*, 473 F.2d 1376, 1378 (5th Cir. 1973) (allowing appeal from remand holding that Secretary of HEW could not prove availability of reasonable job opportunities by testimony of vocational expert who had not interviewed claimant); *Cohen v. Perales*, 412 F.2d 44 (5th Cir. 1969), *rev'd on other grounds sub nom. Richardson v. Perales*, 402 U.S. 389, 91 S.Ct. 1420, 28 L.Ed.2d 842 (1971) (allowing appeal from remand establishing agency standards for the admission of hearsay evidence and holding that hearsay evidence is not substantial evidence to support agency decision).

Second, the district court's order is final as to these issues. There are no further steps that the government can take to avoid imposition of the procedural requirements it seeks to challenge here. *See Abney v. United States*, 431 U.S. 651, 659, 97 S.Ct. 2034, 2040, 52 L.Ed.2d 651 (1977). The district court has unambiguously declared in an order, a subsequent opinion and a denial of a stay motion that it will take no further actions pending FDA compliance with its decree. Its order therefore cannot realistically be characterized as not final because subject to revision. *Compare Coopers & Lybrand v. Livesay*, 437 U.S. 463, 469, 98 S.Ct. 2454, 2458, 57 L.Ed.2d 351 (1978); *Eluska v. Andrus*, 587 F.2d 996, 1001 (9th Cir. 1978). The district court's retention of jurisdiction over the case does not affect the finality of its order. *Compare United Transpor-*

tation Union v. Illinois Central R.R., 433 F.2d 566, 568 (7th Cir. 1970), *cert. denied*, 402 U.S. 915, 91 S.Ct. 1374, 28 L.Ed.2d 661 (1971), *with Transportation-Communication Division, Brotherhood of Railway, Airline & Steamship Clerks v. St. Louis-San Francisco Ry.*, 419 F.2d 933, 936 (8th Cir. 1969), *cert. denied*, 400 U.S. 818, 91 S.Ct. 34, 27 L.Ed.2d 45 (1970).

Third, review of the remand order is urgent, for if we lack jurisdiction now over the questions presented, it seems improbable that they will ever be subject to review. *Compare Gueory, supra*, 510 F.2d at 1225 *and Gold, supra*, 473 F.2d at 1378 *and Perales, supra*, 412 F.2d at 48 *with Coopers & Lybrand, supra*, 437 U.S. at 469, 98 S.Ct. at 2458 *and Loya v. INS*, 583 F.2d 1110 (9th Cir. 1978) *and Barfield v. Weinberger*, 485 F.2d 696 (5th Cir. 1973).

Fourth and finally, the characteristic of importance is also present here.

> "Importance in this context refers to the scope of precedential value—to whether a case presents 'an important and unsettled question of controlling law', *United States v. Sorren, supra*, 605 F.2d at 1213, a decision as to which 'will settle the matter not simply for the case at hand but for many others'. *Grinnell Corp. v. Hackett, supra*, 519 F.2d at 597."

Continental Investment Corp., supra, at 6. The government's appeal does not merely challenge an exercise of the district court's discretion, *see In re Grand Jury Proceedings*, 580 F.2d 13, 17 (1st Cir. 1978); instead, it raises broader questions of how FDA enforcement actions are to proceed. Resolution of these questions is important both to the future FDA regulatory efforts and to the public, whose safety may depend upon those efforts. We therefore proceed to the merits of the government's contentions.[2]

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[2] As to the appeal in general, Alcon argues that we are deprived of

The district court premised its decision to remand to the FDA on interrelated procedural and substantive grounds. The court was troubled by the agency's failure to conduct "a formal administrative determination of the 'new drug' status of WANS" before instituting suit against Alcon. In the absence of such a determination, the court felt that an FDA internal regulation—Compliance Policy Guide 7132c.08—precluded enforcement action against WANS unless the agency possessed "significant new information which questions the safety of the drug." However, the court characterized itself as ill-suited to decide the "new drug" status of WANS or to determine whether "significant new information" existed that questioned WANS' safety. Citing lack of jurisdiction, the doctrine of primary agency jurisdiction and prudential considerations, the court decided that these questions were better left to "the

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jurisdiction by 28 U.S.C. § 2105, which provides

> There shall be no reversal in the Supreme Court or a court of appeals for error in ruling upon matters in abatement which do not involve jurisdiction.

Passing by the question whether this action is in abatement, we note that the district court's remand order can be understood as involving jurisdiction, *see Aetna State Bank v. Altheimer*, 480 F.2d 750, 753 (7th Cir. 1970), and our disposition of the case is not, technically, a "reversal," *see* 15 Wright, Miller & Cooper, *Federal Practice & Procedure: Civil* § 3903, at 414-15 (1976). In any event, despite its plain language section 2105 has never been interpreted as a significant limitation on federal appellate jurisdiction:

> "The most important feature of § 2105 is certainly its disuse.
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> • • • • • •
>
> "[A]ppellate review . . . is notoriously frequent with respect to such problems as abstention of federal decision in deference to state proceedings, deferral of judicial decision pending resort to the primary jurisdiction of administrative agencies, or a requirement that private grievance proceedings be exhausted before seeking judicial interference in labor-management relations."

15 Wright, Miller & Cooper, *supra*, § 3903, at 414.

Agency entrusted by Congress with the necessary expertise to make a responsible determination." Accordingly, it ordered the action "remanded to the Food and Drug Administration to hold a formal administrative hearing pursuant to 5 U.S.C. § 554 on the issue as to whether WANS is a 'new drug' in conformity with the enforcement priorities enunciated in F.D.A.'s Compliance Policy Guide 7132c.08."

The court's concern over summary institution of enforcement proceedings is shared by some in the drug industry, *see* Swire, FDA's Multiple Seizure Powers: A Time for Equity, 34 Food, Drug, Cosmetic L.J. 244 (1979), but the imposition of a pre-enforcement hearing requirement (coupled with preliminary relief, as, to be meaningful, it would have to be) is at odds with the language and intent of the Act. To be sure, in certain circumstances a formal administrative proceeding is a precondition to agency action. For example, when the FDA issues, pursuant to 5 U.S.C. § 554(e), a declaratory order governing all drugs covered by a particular new drug application, or when it withdraws approval of a new drug application pursuant to 21 U.S.C. § 355(e), it must first hold a hearing in compliance with section 554 of the Administrative Procedure Act, 5 U.S.C. § 554. *See Hynson, supra*, 412 U.S. at 620, 625, 93 S.Ct. at 2478, 2480. Each action is a "case of adjudication required by statute to be determined on the record after opportunity for an agency hearing" for purposes of the APA, 5 U.S.C. §554(a). *See* 5 U.S.C. § 554(e) (declaratory order); 21 U.S.C. § 355(e) (withdrawal of NDA). By contrast, there is no statutory hearing requirement for FDA decisions to initiate seizure or injunction actions. *See* 21 U.S.C. §§ 332, 334. Indeed, the probable cause determination necessary to institute multiple seizure actions against allegedly misbranded products is to be made "without hearing." 21 U.S.C. § 334(a)(1). As the Supreme Court has made abundantly clear, a manu-

facturer subjected to an FDA enforcement action has no right to raise objections in an administrative forum prior to the agency's institution of the action. *See Ewing, supra,* 339 U.S. 594, 70 S.Ct. 870, 94 L.Ed. 1088. *Cf. Abbott Laboratoris v. Gardner,* 387 U.S. 136, 146-48, 87 S.Ct. 1507, 1514-15, 18 L.Ed.2d 681 (1967) (reaffirming *Ewing* and distinguishing it from declaratory action brought by drug manufacturers challenging FDA regulations prior to their enforcement. This is because the imposition of any formal, pre-enforcement hearing requirement might seriously impair the effectiveness of the Act's enforcement provisions. *See id.*

The district court's concern that the FDA might be proceeding in violation of its own internal regulatory guidelines was also in error. Compliance Policy Guide 7132c.08 establishes FDA enforcement priorities for specific types of drugs, *see infra,* and declares that the FDA will depart from those priorities only under specified circumstances, one being receipt of "significant new information which questions the safety or effectiveness of the drug." A brief review of the history [3] and text of Compliance Policy Guide 7132c.08, however, demonstrates that the guideline does not apply to WANS.

Under the 1938 Federal Food, Drug, and Cosmetic Act, a drug had only to be proven safe to be approved by the FDA for interstate marketing. Approval of a new drug application was automatic within a fixed period after submission unless the FDA in the interim affirmatively dis-

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[3] Our discussion draws on several sources: *United States v. Lannett Co.,* 585 F.2d 575 (3d Cir. 1978); *Hoffman-LaRoche, Inc. v. Weinberger,* 425 F.Supp. 890 (D.D.C. 1975); Fleshner, *Lannett,* Premarketing Clearance and "Me-Too" Drugs: Where Do We Go From Here?, 35 Food, Drug, Cosmetic L.J. 44 (1980). Note, Regulating Laetrile: Constitutional and Statutory Implications, 5 U.Dayton L.Rev. 155 (1980); Note, New Drug Approval: *Lannett,* The Drug Lag, and the NDA System, 11 Rut-Cam. L.J. 231 (1980).

approved it. The 1962 amendments to the Act substantially modified these premarketing clearance procedures. A "new drug" was redefined to be one not generally recognized among experts as *effective* as well as safe, and the automatic approval of new drug applications was eliminated. A "new drug" therefore could not be lawfully marketed unless it satisfied both the safety *and* effectiveness requirements of the Act and had been affirmatively approved by the FDA. These changes presented the FDA with an enormous problem: By virtue of the 1962 amendments thousands of drugs with NDA's already approved for safety, but not effectiveness ("pioneer" drugs), and many more thousands of drugs considered generically identical to already approved drugs ("me-too" drugs), became "new drugs" subject to the agency clearance procedure of section 505 of the Act, 21 U.S.C. § 355. To speed its newly created job of determining the effectiveness of these drugs, the FDA arranged to have the National Academy of Sciences-National Research Council conduct a Drug Efficiency Study of nearly 4,000 drugs. The results of this study were incorporated into Drug Efficiency Study Implementation (DESI) notices that indicated whether or not the FDA considered particular drugs to be effective. All distributors of drugs covered by a DESI notice and not holding an approved new drug application were variously required to submit either a full or abbreviated new drug application. However, upon submission and prior to approval of the required application, manufacturers of me-too drugs were permitted to market their products if a full new drug application had already been approved for the related pioneer drug. This approach to the administrative problems created by the 1962 amendments was struck down in *Hoffmann-LaRoche, Inc. v. Weinberger*, 425 F.Supp. 890 (D.D.C. 1975), which held that *no* new drug—pioneer or me-too—could be introduced into interstate commerce without its new drug application having first been approved by the FDA.

Compliance Policy Guide 7132c.08 is the FDA's attempt to incorporate into the DESI program the holding of *Hoffmann-LaRoche*. Recognizing that independent evaluation of the effectiveness of all DESI drugs will unavoidably delay achievement of industry-wide compliance with the Act, the Guide sets out "a strategy to deal on a priority basis with those drugs which most affect public health and safety[,] to provide equitable treatment among competing firms, and to have a maximum impact on violative products." It establishes FDA enforcement priorities according to two general groups of drugs: "DESI prescription drugs where a final determination on effectiveness has been made" and "DESI and other prescription drugs where a final determination on effectiveness has not been made." Each group is further divided into several smaller categories.

WANS is not covered by Compliance Policy Guide 7132c.08 because it is not part of the DESI program. As Alcon expressly acknowledges, WANS is neither a pioneer drug (it is not covered by a pre-1962 NDA) nor a me-too drug (it is not generically identical to a pioneer drug). To read the phrase "other prescription drugs where a final determination on effectiveness has not been made," *supra*, as including WANS would impermissibly extend the Compliance Policy Guide far beyond its historic context and purpose. The proper scope of the second group of drugs defined by the Compliance Policy Guide is illustrated by its three subcategories, none of which applies to WANS. It is true, as Alcon points out, that the FDA's initial regulatory letter described WANS as falling under this category, but later correspondence omitted this reference. In any event, Alcon does not claim that what the government concedes to have been an unfortunate mistake might now estop it from correctly treating WANS as a drug not covered by the Guide. The district court was thus in error to require that the FDA comply with Compliance Policy

Guide 7132c.08 and withhold regulatory action against WANS in the absence of "significant new information which questions the safety or effectiveness of the drug."

Finally, we turn to the district court's belief that it lacked, or should not have exercised, jurisdiction over the "new drug" and "grandfather clause" questions in this case. The court's declaration that "[i]t is not within the jurisdiction of this Court to determine whether the drug in issue is or is not a new drug" is plainly incorrect. Jurisdiction over the new drug issue is shared by the FDA, *see Weinberger v. Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 653, 93 S.Ct. 2488, 2494, 37 L.Ed.2d 235 (1973); *Hynson, supra*, 412 U.S. at 624, 93 S.Ct. at 2480, and the federal district courts, *see CIBA Corp. v. Weinberger*, 412 U.S. 640, 644, 93 S.Ct. 2495, 2498, 37 L.Ed.2d 230 (1973); *Premo Pharmaceutical, supra*, 629 F2d at 801; *United States v. "X OTAG Plus Tablets"*, 602 F.2d 1387 (10th Cir. 1979); *United States v. Mosinee Research Corp.*, 583 F.2d 930, 931-32 (7th Cir. 1978).

Further, the district court's invocation of the doctrine of "primary jurisdiction" to justify its refusal to exercise its own jurisdiction is not persuasive. As we have elsewhere stated, deference to an agency's primary jurisdiction makes little sense in the context of an enforcement proceeding initiated by the agency. *ICC v. B & T Transportation Co.*, 613 F.2d 1182, 1187 (1st Cir. 1980). This is especially true where, as here, a party remains subject to the agency's regulatory efforts despite the remand. We have held above that a district court lacks the power to require the FDA to defer seizures *pendente lite* or to order release of seized drugs prior to a determination of the merits of the agency's claims. The effect of a remand to the agency thus would hardly be beneficial to the product's manufacturer. Without the relief afforded by the other aspects of the district court's order, Alcon would be deprived of a judicial remedy in return for an administra-

tive procedure of uncertain duration before an unsympathetic agency. We would be surprised if either Alcon or the district court would be content with a remand under such circumstances. With this consideraton in mind, and in view of the fact that the FDA's current position on the "new drug" status of WANS is already clear; that the FDA carries the burden of proving its position at trial; and that the agency has no duty to hold a pre-enforcement hearing or to justify its action under its Compliance Policy Guide, *see supra,* we do not see what would be gained in this case by a remand. At least it can be said that two fundamental purposes of deference to agency jurisdiction—"coordinating administrative and judicial machinery" and assuring uniformity of regulation, *Mashpee Tribe v. New Seabury Corp.*, 592 F.2d 575, 580 (1st Cir.), *cert. denied,* 444 U.S. 866, 100 S.Ct. 138, 62 L.Ed.2d 90 (1979—would not be served by the district court's order. *See generally Litton Systems, Inc. v. Southwestern Bell Telephone Co.,* 539 F.2d 418 (5th Cir. 1976); *Mississippi Power & Light Co. v. United Gas Pipe Line Co.,* 532 F.2d 412 (5th Cir. 1976), *cert. denied,* 429 U.S. 1094, 97 S.Ct. 1109, 51 L.Ed.2d 541 (1977); *ICC v. All-American, Inc.,* 505 F.2d 1360, 1362-64 (7th Cir. 1974).

This is not to say that a remand in the context of enforcement proceedings might never be appropriate. In *Bentex Pharmaceuticals, supra,* 412 U.S. 645, 93 S.Ct. 2488, 37 L.Ed.2d 235, the Supreme Court upheld the power of a district court to refer to the FDA "new drug" and "grandfather clause" issues initially presented to the court in a declaratory judgment action instituted by drug manufacturers. The Court went on to note that a court could stay its hand "[e]ven where no . . . administrative determination has been made and the issue arises in a district court in enforcement proceedings. . . ." 412 U.S. at 652, 93 S.Ct. at 2493. This observation, however, should be understood in relation to the situation in *Bentex,* where some 21 drug

manufacturers had requested declaratory relief. There the court was in essence being asked to issue, without benefit of prior administrative proceedings, a decision upon whether a substantial portion of an industry was complying with the Act. Here the district court is being asked only to decide whether a single drug manufactured by a single company is being marketed illegally. The agency's view of the question is clear and will have to be substantiated for the agency to prevail in court. We therefore conclude that under *Bentex* this is not an appropriate case for a remand.

As the district court recognized, a third purpose of the doctrine of primary jurisdiction—taking advantage "of agencies' special expertise," *Mashpee Tribe, supra,* 592 F.2d at 580—weighs in favor of a remand, but not, we think, decisively. The Supreme Court has described the "new drug" and "grandfather clause" issues as "the kinds of issues peculiarly suited to initial determinaton by the FDA." *Bentex Pharmaceuticals, supra,* 412 U.S. at 653, 93 S.Ct. at 2494. Neverthless, contrary to the Court's suggestion it has not been "commonplace" for courts to await an appropriate administrative declaration in enforcement proceedings. *Bentex, supra,* 412 U.S. at 652, 93 S.Ct. at 2493; lower courts continue to hear and decide the "new drug" status of drugs challenged by the FDA in seizure and injunction actions. *See, e. g., Premo Pharmaceuticals, supra.* 629 F.2d at 804-05 (issue decided by the court of appeals): *"X OTAG Plus Tablets", supra,* 602 F.2d 1387; *Mosinee Research, supra,* 583 F.2d 930; *United States v. Articles of Drug . . . Horomin,* 498 F. Supp. 424 (D.N.J. 1980). The government asserts, and we have found nothing to the contrary, that of the hundreds of enforcement actions brought by the FDA under section 505 since 1938, none save the present has been remanded to the agency. Returning issues in an enforcement action to the FDA imposes an administrative burden for which

the Act makes no provision, and insofar as the procedure delays adjudication of the regulatory status of a drug, may work to the disadvantage not only of the agency and the public, but also of the manufacturer. In such circumstances the power to remand must be used sparingly. Had the trial set for May 1979 been held, WANS' status would long since have been laid to rest. In deciding the case, the FDA's expertise would have been available to the court, in that to sustain its burden the agency would have had to present expert evidence establishing its claims regarding WANS. We therefore conclude that the district court erred in remanding the case to the FDA.

The orders of the district court are vacated and the case is remanded for further proceedings consistent with this opinion.

APPENDIX G

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF PUERTO RICO

VERDICT

CONSOLIDATED CASES

Civ. No. 78-1830 (JP)

UNITED STATES OF AMERICA, *Plaintiff*

vs.

ARTICLES OF DRUG CONSISTING OF 13,522 BOXES OF WANS NO. 1, ETC., *Defendant*

Civ. No. 78-2378 (JP)

UNITED STATES OF AMERICA, *Plaintiff*

vs.

ALCON LABORATORIES (P.R.), INC., a corporation; EDGAR H. SCHOLLMAIER and JOHN W. FEIK, individuals, etc., *Defendants*

Civ. No. 80-0243 (JP)

UNITED STATES OF AMERICA, *Plaintiff*

vs.

ARTICLES OF DRUG CONSISTING OF 5,047 BOXES OF WANS NO. 1 AND 2,534 BOXES OF WANS NO. 2, ETC., *Defendants*

Civil No. 80-2112 (JP)

UNITED STATES OF AMERICA, *Plaintiff*

vs.

ARTICLES OF DRUG CONSISTING OF 8,327 BOXES OF WANS NO. 1, ETC., *Defendants*

Civ. No. 82-0055 (JP)

UNITED STATES OF AMERICA, *Plaintiff*

vs.

ARTICLES OF DRUG CONSISTING OF 5,906 BOXES OF WANS NO. 1, ETC., *Defendant*

SPECIAL INTERROGATORIES TO THE JURY

We, the jury, unanimously answer the interrogatories submitted by the Court as follows:

(1) Do you find from a preponderance of the evidence that before October 10, 1962 the WANS products were generally recognized, among experts qualified by scientific training and experience to evaluate the safety of drugs, as being safe for use under the conditions then prescribed, recommended or suggested in their labeling?

Yes X

No _____

(2) Do you find from a preponderance of the evidence that the WANS products are generally recognized, among experts qualified by scientific training and experience to

evaluate the safety of drugs, as being safe for use under the conditions prescribed, recommended or suggested in their labeling at the present time?

Yes X

No _____

(3) Do you find from a preponderance of the evidence that the WANS products are presently intended solely for use under the same conditions prescribed, recommended or suggested in their labeling as was in use on October 9, 1962?

Yes X

No _____

(4) Do you find from a preponderance of the evidence that the WANS products are generally recognized among experts qualified by scientific training and experience to evaluate the effectiveness of drugs, as effective for use under the conditions prescribed, recommended, or suggested in their labeling at the present time?

Yes X

No _____

In San Juan, Puerto Rico, this 18th day of March, 1983.

_____

FOREPERSON

*ATTACHED INSTRUCTIONS AS TO ANSWER

APPENDIX H

Excerpt from "SCRIP World Pharmaceutical News" April 11th, 1983, No. 784.

FDA has new unapproved drug problem

The US FDA, which won what it thought was a "final" victory over unapproved generic drugs in the US Supreme Court on March 22nd (*Scrip* No 780, p 10), has suffered an unexpected reversal on the issue in the US District Court for Puerto Rico. In US v Alcon Laboratories (Puerto Rico), a case that began in 1978, a local jury has decided that Alcon's combination antinausea suppositories, WANS (pyrilamine maleate and sodium pentobarbital), which have never received NDA approval, are both "grandfathered" under the Food, Drug and Cosmetic Act and thus exempt from NDA requirements, and generally recognised by experts as being safe and effective, further exempting them from any need to obtain explicit FDA marketing approval.

Scrip's Washington correspondent says the FDA has asked the trial judge to overrule the jury's verdict and find in the agency's favour, on grounds that the jury obviously could not have understood the evidence or the questions presented to it, and that the Supreme Court's March 22nd decision demands a different verdict. If the FDA's request is denied, our correspondent understands that the agency will try to appeal, but it is rare for jury verdicts to be appealed by the US Justice Department. If the jury verdict stands, the FDA is expected to treat it as an aberration, and continue its drug approval and enforcement activities as if nothing had happened.

However, *Scrip*'s correspondent says FDA officials are concerned in case the WANS decision is taken as a precedent by other manufacturers. An internal study by the National Center for Drugs and Biologics has preliminarily estimated that between 10% and 15% of all marketed drug

products are in WANS' category—neither covered by an approved NDA nor the subject of DESI (Drug Efficacy Study Implementation) review governing their compliance with the law. Some of these drugs are believed to command sales in execss of WANS' $2.5 million annually, and could therefore be worth defending in court. Our correspondent says that the WANS decision may prompt manufacturers of such FDA-challenged products to seek jury trials as Alcon did so successfully. "Juries picked off the street simply can't understand all the scientific complexities", a senior official told our correspondent on March 29th. "Depending on the circumstances, they may simply decide to opt for the *status quo*—that is, leaving the product where it is".

APPENDIX I

FOOD AND DRUG ADMINISTRATION
COMPLIANCE POLICY GUIDELINES

Guide 7132c.02

CHAPTER 32c—DRUGS, NDA/IND

SUBJECT

Marketed New Drugs Without Approved NDAs or ANDAs

BACKGROUND

Prior policy under the DESI program had permitted a firm to market a new product upon the *submission* of a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) as long as the new product was identical to a prescription drug product that had been evaluated as "effective". The history and justification for this approach were described in a FEDERAL REGISTER notice published on June 20, 1975 (40 FR 26142, see paragraph I(D)(5) on pp. 26144-45). This policy was challenged and overturned in a lawsuit on July 29, 1975 (*Hoffmann-La Roche* v. *Weinberger,* 425 F.Supp. 890 (D. D.C. 1975)). The Court held that if FDA had declared a prescription drug product to be a "new drug", the agency could not permit any identical, similar, or related product to be marketed without prior *approval* of an NDA or ANDA. The complete text of this decision was published in a FEDERAL REGISTER notice on September 22, 1975 (40 FR 43531). Subsequently, the Court granted certain exceptions to this ruling, but these exceptions are not applicable to DESI effective drugs. The amendment to the Court's order was published in the FEDERAL REGISTER on March 2, 1976 (41 FR 9001). It should be noted

that all drugs in the DESI review are "new drugs" under the law.

As a result of this decision, the agency has reevaluated its policy, the resources available to process NDAs and ANDAs and to handle violations of the law, and the alternative policies which might be used to protect the public health and safety within the requirements of the Federal Food, Drug, and Cosmetic Act. The agency has decided to reaffirm that all products marketed as drugs under the DESI program are new drugs and, therefore, require an approved NDA or ANDA for marketing. In view of the reaffirmation of this policy, the agency must proceed to remove from the market all current DESI-effective prescription products that are not the subjects of approved NDA's or ANDA's, and to prevent in the future the marketing of such unapproved products.

The agency is aware that many firms are marketing products without approved new drug applications that are related to DESI effective prescription drugs. In order to achieve uniform compliance with the Court Order, all violative products must be identified and removed from the market. With the resources presently available for attaining industry-wide compliance, this goal will take several years to achieve. Considering the magnitude of the problem, the limitation on FDA's resources, and the resulting long term period before compliance can be fully attained, the agency has developed a strategy to handle unapproved products on a priority basis. The priorities for enforcement action relate to a particular drug's effect on public health and safety, and are designed to have a maximum impact on violative products and to provide equitable treatment among competing firms. This strategy also integrates with ongoing compliance programs directed at DESI-effective prescription drugs, OTC Category II products, and post-1962 NDA prescription drugs, and anticipated compliance programs directed at DESI-Paragraph XIV pre-

scription drugs (those requiring additional studies before a decision on effectiveness can be made), and pre-1962 new drugs which were not part of DESI.

POLICY

Part A of this section outlines the sequence for regulating drugs for which final determinations have been made regarding their new drug status and for which FEDERAL REGISTER notices have been published requiring ANDA or NDA approval for marketing them. All products within each category will be treated in the same fashion regardless of the size of the firm.

The Center for Drugs and Biologics will implement Part A of this policy by identifying those marketed products which are within the Part A categories named below. The District Offices will then initiate regulatory action against any violative products on the market in accordance with a Compliance Program regarding that specific category of drugs. This procedure will be repeated for each category until overall compliance is achieved. The CDB may from time to time add drugs to any category.

Part B of this section covers the regulation of those drugs for which final determinations regarding their regulatory or legal status have not been made.

A. DESI PRESCRIPTION DRUGS WHERE FINAL DETERMINATIONS ON EFFECTIVENESS HAVE BEEN MADE.

Category I—Ineffective Drugs

These are covered by an ongoing program (C. P. 7352.001) and will remain top priority.

Category II—Bio-Problem Drugs

This category consists of DESI-effective prescription drugs with known or potential bioavailability or bioequivalence problems.

Approximately 171 drug entities have been identified in this group. Regulatory action has already been initiated on those identical drugs identified in the DHHS Publication No. (FDA) 76-3009 (revised 6/76). The General Program (C.P. 7352.002) covering this category has issued and follow-up to this category is ongoing under Compliance Program Circular PC 7352.002D.

Category III—Top 200 Prescription Drugs

This category consists of the "Top 200" most widely prescribed drugs that have been DESI-rated as effective. This category does not include antibiotics, topical preparations, and those drugs listed in Categories I and II.

An initial survey indicated that there were approximately 25 drug entities in this category requiring attention. These "Top 200 Prescription Drugs" are identified in Program Circular 7352.002E. Regulatory Letters have issued from District offices to all known manufacturers of unapproved drugs subject to this category.

Category IV—Bio-Related Drugs

This category consists of all the prescription drugs related to those in Category II (i.e., drugs containing one or more of the listed ingredients). This category includes combinations, related chemical forms and related dosage forms, including controlled release. It excludes topical preparations. Controlled release preparations may warrant separate attention but this requires further evaluation. These "bio-related drugs" have been handled under Program Circular 7352.002C and regulatory letters have issued to all known manufacturers of unapproved drugs subject to this category.

Category V—Other Identical DESI-Effective Prescription Drugs

This category consists of those products that are identical to DESI-effective prescription drugs, excluding topical preparations, and are not covered by the preceding categories. These products will be handled under a Compliance Program similar to that used for Category II.

Category VI—Other Related DESI-Effective Prescription Drugs

This category consists of combinations and related chemical dosage forms including controlled release. It excludes topical preparations. Products subject to this category will be handled under a Compliance Program similar to that used for Category II.

Category VII—DESI Effective Prescription Topic Preparations Identical and Related

This category consists of all the topical preparations for the drugs covered in Categories I-VI. These products will be handled under a Compliance Program similar to that used for Category II.

B. DESI AND OTHER PRE-1962 PRESCRIPTION DRUGS WHERE FINAL DETERMINATIONS ON THEIR REGULATORY OR LEGAL STATUS HAVE NOT BEEN MADE.

These drugs are covered by the categories outlined below and may be worked into the regulatory scheme described under Part A above as final determinations are made regarding their effectiveness, new drug status, or grandfather status.

DESI "Paragraph XIV" Prescription Drugs.

This category consists of prescription drugs that are currently exempted from regulatory action under

Judge Bryant's Order. As final determinations are made regarding the effectiveness of these drugs, they will be handled under the appropriate Part A category on a continuing basis. That is, if a drug is downgraded to "ineffective" it will be handled under Category I, and if it is upgraded to "effective" it will be handled under one of the remaining Part A categories.

DESI "Less-Than-Effective" Prescription Drugs.

This category consists of prescription drugs for which final DESI determinations on effectiveness have not been made (e.g., possibly or probably effective drugs and those with current NOHs), other than those in the Paragraph XIV Category. As final determinations are made regarding the effectiveness of these drugs, they will be handled under the appropriate Part A category on a continuing basis.

Pre-1962 Presciption Drugs Covered by an NDA But Not Yet Reviewed by DESI.

A certain number of drugs covered by pre-1962 NDA's have not undergone a DESI review. Procedures are being implemented so that these drugs will be evaluated to determine their effectiveness. As final determinations are made on these drugs, they will be handled under the appropriate Part A category on a continuing basis.

Pre-1962 Prescription Drugs Not Covered by an NDA.

A certain number of drug products containing one or more active ingredients first introduced into the marketplace before 1962 are not covered by an NDA. These products are marketed based on their manufacturers' belief that such products are not subject to the new drug provisions of the act. Procedures will be implemented so that these products will be evalu-

ated to determine whether the new drug provisions are applicable to them. If a final determination is made that a particular drug in this category requires an approved NDA or ANDA before marketing, the drug will be handled under the appropriate Part A category on a continuing basis.

POLICY GUIDELINE EXCEPTIONS

While this policy guide represents a systematic approach to the implementation of the Court Order and the requirements of the new drug provisions of the act, it is not meant to preclude taking action against drugs outside of the established priorities under the following circumstances:

1. Including a new drug (505) charge (where appropriate) for a drug subject to this policy which becomes violative under another provision of the act.
2. Initiating regulatory action (as a new drug) against any drug subject to this policy should the agency receive significant new information which questions the safety or effectiveness of the drug.
3. Initiating regulatory action against any drug on the market without an approved new drug application if it is identical or related to a post-1962 NDA approved for safety and effectiveness or it contains a new chemical entity not previously marketed.
4. Initiating regulatory action against an unapproved prescription drug product first marketed after November 13, 1984, if the product differs from a product covered by Part B above in:
    a. formulation (as described below);
    b. dosage or strength;
    c. dosage form;
    d. route of administration;

e. indications for use; or

f. intended patient population.

A formulation will be considered different, if:

(1) the product contains a different active ingredient;

(2) the product contains a different quantity of an active ingredient;

(3) the product is a non-oral dosage form other than a topical preparation and it contains one or more different inactive ingredients, different amounts of inactive ingredients, or different proportions of inactive ingredients to the extent that the names, amounts, or proportions of inactive ingredients are required by regulation to be disclosed in labeling (see 21 CFR 201.100(b)(5)); or

(4) the product is an oral dosage form or a topical preparation and it contains one or more inactive ingredients not customarily used in such a product.

Differences that result from compliance with a compendial standard or an FDA requirement will not cause a product to be subject to this exception.

5. Initiating regulatory action against an unapproved prescription drug product covered by Part B above, if after November 13, 1984, a change is made in:

a. the product's formulation (as described below);

b. the product's dosage or strength;

c. the product's dosage form;

d. the product's route of administration;

e. the product's indications for use; or

f. the product's intended patient population.

A formulation will be considered different, if:

(1) the product contains a different active ingredient;

(2) the product contains a different quantity of an active ingredient;

(3) the product is a non-oral dosage form other than a topical preparation and it contains one or more different inactive ingredients, different amounts of inactive ingredients, or different proportions of inactive ingredients to the extent that the names, amounts, or proportions of inactive ingredients are required by regulation to be disclosed in labeling (see 21 CFR 201.100(b)(5)); or

(4) the product is an oral dosage form or a topical preparation and it contains one or more inactive ingredients not customarily used in such a product.

Changes that are made to comply with a compendial standard or an FDA requirement will not cause a product to be subject to this exception.

Aside from the exceptions mentioned above, the agency will adhere to the priorities as established. In addition, the CDB will deny FDA approval for contract purchase by other Federal government agencies (DOD, VA, PHS) of any drug subject to this policy which does not have an approved NDA or ANDA.

Originally published 10/06/76 as 7132c.08
Revised: 04/01/81
Revised: 09/19/84

APPENDIX J

Package Insert for WANS' Labeling (1962)

ANTI-NAUSEA SUPPRETTES®

COMPOSITION: Children (Blue), (Scored for ½ dosages), Pyrilamine Maleate 25 mg. and pentobarbital sodium* ½ gr. (30 mg.).

No. 1 *(Adults)* (Pink) Pyrilamine Maleate 50 mg. and pentobarbital sodium* ¾ gr. (45 mg.).

No. 2 *(Adults)* (Yellow) Pyrilamine Maleate 50 mg. and pentobarbital sodium* 1½ gr. (100 mg.). In Webster's exclusive NEOCERA BASE.

*Warning: may be habit forming.

ACTION AND USES: Unsurpassed for prevention as well as control of nausea and/or vomiting regardless of emetic stimuli. Effectiveness due to the synergistic actions of the antihistamine, pyrilamine maleate and the short acting sedative, pentobarbital sodium. Especially effective in all indications where either antihistamines or barbiturates alone are of value. Adsorption from the Neocera Base is equal to oral absorption of equipotent doses.

ADMINISTRATION AND DOSAGE: Children, under 2 yrs. of age ½ Anti-Nausea Supprette, rectally, every 6 to 8 hours; 2 to 12 yrs. of age one Supprette, rectally, every 6 to 8 hours. *Adults,* one No. 1 Supprette to inhibit mild nausea and/or vomiting; one No. 2 Supprette to stop pernicious vomiting. Adult doses: repeat 4 to 6 hours. Moisten before inserting.

SIDE EFFECTS: Some degree of drowsiness may result which is usually desirable.

PRECAUTIONS: Use with caution in cerebral arteriosclerosis and mental disturbances.

CONTRAINDICATIONS: Severely impaired hepatic function.

HOW SUPPLIED: In Glass Jars of 12. Do Not refrigerate.

LITERATURE AVAILABLE: Yes.

APPENDIX K

Package Insert For WANS' Labeling (1978)

WANS®
(Pyrilamine Maleate and Pentobarbital Sodium)
Anti-Nausea Supprettes

DESCRIPTION: WANS® is a combination of an antihistamine (Pyrilamine Maleate) and a sedative (Pentobarbital Sodium) in suppository form for rectal administration.

Each WANS® SUPPRETTE• contains (in water-soluble Neocera® Base): WANS® Children (blue): Pyrilamine Maleate 25 mg and Pentobarbitol Sodium• 30 mg; scored for ½ dosage.

WANS® No. 1 (pink): Pyrilamine Maleate 50 mg and Pentobarbital Sodium• 50 mg; scored for ½ dosage.

WANS® No. 2 (yellow): Pyrilamine 50 mg and Pentobarbital Sodium• 100 mg; scored for ½ dosage.

•WARNING: May be habit forming.

The Neocera Base is a blend of Polyethylene Glycol 400, 1540, and 6000, Polysorbate 60 and color additives including FD&C Yellow No. 5 (Tartazine) in WANS No. 2. The structural formulas for the active ingredients are:

Established name:
Pyrilamine Maleate:

Chemical name:
1,2-Ethanediamine, *N*-[(4-methoxyphenyl)methyl]-*N'*,*N'*-dimethyl-N-2-pyridinyl-, (Z)-2-butenedioate (1:1).

Established name:
Pentobarbital Sodium:

Chemical name:
2,4,6(1*H*,3*H*,5*H*)-Pyrimidinetrione, 5-ethyl-5-(1-methylbutyl)-monosodium salt.

CLINICAL PHARMACOLOGY: Pyrilamine maleate is an antihistamine of the ethylenediamine family, which exhibits recognized antiemetic activity. Pyrilamine maleate may exhibit a noticeable stimulating effect on the central nervous system (CNS) and, on occasion, a weak CNS-depressant effect.

Pentobarbital sodium is an effective, short-acting barbiturate which acts as a general CNS-depressant. Pentobarbital sodium suppresses the vomiting center itself, and at the same time, provides sedation.

INDICATIONS AND USAGE: WANS® is indicated in the symptomatic treatment of nausea and vomiting. The suppository dosage form is a particularly useful method of drug administration in patients with nausea and vomiting who are unable to retain oral medication.

CONTRAINDICATIONS: Acute intermittent porphyna, known hypersensitivity to barbiturates or antihistamines, known barbiturate addiction, in senility, severe hepatic impairment and in the presence of uncontrolled pain, acute head injury associated with vomiting or other signs of CNS injury. Not for use in infants under six months of age since they are more sensitive to the central nervous system stimulating effects of pyrilamine maleate than adults. Pyrilamine maleate may cause convulsions in infants, particularly in excessive dosage.

WARNINGS:

Caution should be exercised when administering WANS® to children for the treatment of vomiting. Antiemetics are not recommended for treatment of uncomplicated vomiting in children and their use should be limited to prolonged vomiting of known etiology. There are three principal reasons for caution:

1. There have been some recent reports of toxic encephalopathy, characterized by a depressed level of consciousness, marked irritability and ataxia in infants and children following administration of higher-than-recommended doses of pyrilamine maleate and pentobarbital sodium combination products such as WANS®. The recommended dosage should therefore not be exceeded.
2. There has been some suspicion that centrally acting antiemetics may contribute, in combination with viral illnesses (a possible cause of vomiting in children), to development of Reye's syndrome, a potentially fatal, acute childhood encephalopathy with visceral fatty degeneration, especially involving the liver. Although there is no confirmation of this suspicion, caution is nevertheless recommended.
3. It should also be noted that salicylates and acetaminophen are hepatotoxic at large doses. Although it is not known that at usual doses they would represent a hazard in patients with the underlying hepatic disorder of Reye's syndrome, these drugs should be avoided in children whose signs and symptoms could represent Reye's syndrome, unless alternative methods of controlling fever are not successful.

Barbiturates may be habit forming. Administration in the presence of pre-existing psychologic disturbances may result in confusion, delirium, and accentuation of symp-

toms. Idiosyncratic reactions may occur and include lassitude, vertigo, nausea, vomiting, and diarrhea. Acquired sensitivity to barbiturates may result in allergic reactions including urticaria, dermatitis, and rarely, extoliative dermatitis and degenerative changes in the liver and kidney.

Pentobarbital sodium may cause fetal harm when administered to a pregnant woman. Pentobarbital sodium, can cross the placental barrier and may depress the fetal central nervous system so that respiration is not adequately established at birth. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS:

General: WANS® should be administered with caution to patients with a history of drug dependence or suicidal tendencies. Caution should be exercised when the drug is used concurrently with other sedative, hypnotic, or narcotic agents. This drug should be given with caution to patients with known acute or chronic hepatic disease, fever, hyperthydroidism, diabetes mellitus, severe anemia, and congestive heart failure.

WANS® No. 2 contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of sensitivity to FD&C Yellow No. 5 (tartrazine) in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Information for Patients: Do not take alcoholic beverages or other CNS depressants while taking this product. This product may cause drowsiness. Do not drive, operate machinery, or otherwise engage in activities where impair-

ment of alertness and coordination could result in accidents or injury.

Drug Interactions: Alcohol and other CNS depressants taken in conjunction with this product produce an additive depressant effect on the central nervous system. Patients taking other CNS depressants concomitantly with this product should be observed more frequently, especially during the initiation of therapy. Also, barbiturates and antihistamines must be used with caution in patients receiving monoamine oxidase inhibitors since these drugs may potentiate the depressant effect of the barbiturate or augment the anticholinergic effect of the antihistamine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate the carcinogenic potential of this drug have not been performed. There is no evidence in the published literature that the ingredients of this product are carcinogenic, mutagenic, or impair fertility.

Pregnancy:

Teratogenic Effects: Pregnancy Category D. See "Warnings" section.

Non Teratogenic Effects: Dependence of the mother on pentobarbital sodium may result in withdrawal symptoms (e.g., hyperirritability, vomiting, shrill cry) in the baby after delivery.

Nursing Mothers: Antihistamines may inhibit lactation and may be excreted in breast milk. Since the risk of adverse reactions is higher in infants, use of antihistamines is not recommended in nursing mothers. Barbiturates may also be excreted in breast milk. The effects of barbiturates in the nursing infant may include sedation and induction of hepatic metabolizing enzymes. Therefore, because of the potential for serious adverse reactions in nursing infants from the use of this product, a decision should be

made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: See "Contraindications" and "Warnings" section for information regarding the use of this product in infants and children.

ADVERSE REACTIONS: Antihistamine side effects include drowsiness, potentiation of the sedative effect of barbiturates, fatigue, vertigo, incoordination, tremor, muscle weakness, dryness of the nose, mouth, and throat, tinnitus, pupiliary dilation and blurred vision, urinary retention, impotence, epigastric and intestinal pain, anorexa, nausea, vomiting, diarrhea, excitation, euphonia, insomnia, nervousness, palpitation, tachycardia, hypotension, hypersensitivity reactions such as allergic dermatitis, and rarely blood dyscrasias. Side effects associated with barbiturates include drowsiness, lethargy, sedation, paradoxic restlessness or excitement in susceptible persons, respiratory depression, coma, and delinum.

DRUG ABUSE AND DEPENDENCE:

Controlled Substance: WANS® is a Schedule III controlled drug.

Dependence: As with other CNS-depressants, the use of pentobarbital sodium may induce a psychological dependence in some patients. Prolonged, uninterrupted use of barbiturates, even in therapeutic doses, may result in physical and psychological dependence. The symptoms of chronic intoxication are similar to those of alcohol intoxication (e.g., disorientation, ataxia, euphoria). In such cases, abrupt discontinuance may precipitate typical withdrawal symptoms, including convulsions. Therefore, the drug should be withdrawn gradually.

Abuse: Those persons who develop a psychological dependence on pentobarbital sodium may increase the dosage

without consulting a physician and may subsequently develop a physical dependence on the drug.

OVERDOSAGE: Antihistamine overdosage, particularly in children, may result in hallucination, excitement, ataxia, incoordination, athetosis, convulsions and death. Mechanican ventilation and supportive care are important, and drugs likely to potentiate the effects of the antihistamine should not be given.

Overdosage of pentobarbital sodium is manifested by drowsiness, lethargy, sedation, paradoxic restlessness or excitement in susceptible persons, respiratory depression, delinum, hypothermia, latent fever, slugglishness or absence of reflexes, coma, gradual appearance of circulatory collapse, pulmonary edema and death. Supportive care is of primary importance in the treatment of barbiturate overdosage.

1. Maintain and assist respiration as indicated.
2. Support circulation with vasopressors and intravenous fluids as required.
3. Aspirate stomach contents, taking care to avoid pulmonary aspiration.
4. Use osmotic diuretic and measure intake and output of fluids.

In severe overdosage, hemodialysis may be lifesaving, especially if a vigorous diuresis cannot be maintained.

DOSAGE AND ADMINISTRATION:

Children: For children 2 to 12 years of age (over 15 kg bodyweight) the usual dose is one WANS® CHILDREN, rectally, every 6 to 8 hours as required. Do not exceed three doses in 24 hours. Children 6 months to 2 years of age (less than 15 kg body weight) should use not more than ½ the above dosage. Do not use in infants below the

age of 6 months. In determining the optimum dosage in infants and children, consideration should be given in each case to the age and weight of the patient, the etiology and severity of the conditions being treated and the clinical response. The above recommended dosages should not be exceeded (see "Warnings").

Adults: Rectally, one WANS® No. 1 to inhibit mild nausea and/or vomiting or one WANS® No. 2 to control pernicious vomiting. Repeat doses for adults should be 4 to 6 hours apart; do not exceed four doses in 24 hours. The optimum dosage must be determined in each case by the clinical response. Moisten finger and SUPPRETTE® with water before inserting.

HOW SUPPLIED: In foil strip packaged units of 12 (scored for ½ dosage).

WANS® CHILDREN (blue): NDC 0991-1000-75

WANS® No. 1 (pink): NDC 0991-1001-75

WANS® No. 2 (yellow): NDC 0991-1002-75

STORAGE: Store at room temperature. Do not refrigerate.

ALCON LABORATORIES (PUERTO RICO) INC.
Humacao, Puerto Rico 00661

APPENDIX L

Excerpt from the Government's Brief on the Merits in the First Circuit Court of Appeals

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5. TESTIMONY CONCERNING ACTUAL SAFETY OR EFFECTIVENESS IS NOT RELEVANT TO THE ISSUE OF GENERAL RECOGNITION

The actual safety and effectiveness of the WANS products was not an issue, and the jury was so instructed. [Trial Trans. Vol. VII at 51] J.A. 604. *See, e.g., Premo*, 629 F.2d at 803; *Hormonin*, 498 F. Supp. at 431.[27] Nevertheless, the district court admitted the testimony of Dr. Eileen Barker, an FDA medical officer who was Executive Secretary of the 1977 FDA advisory committee that brought the WANS products and other products with the same active ingredients to the agency's attention. Over the government's objection, the court permitted Alcon to elicit testimony from Dr. Barker, as a hostile witness, about the proceedings of the advisory panel and the absence of any reports of fatalities associated with the use of WANS or similar products. [Trial Trans. Vol. IV at 52-54] J.A. 393-95.

Because Dr. Barker's testimony was irrelevant, its admission was erroneous. Its admission was not merely harmless error, but by its very nature was unfairly prejudicial to the government's case because it caused the jury and the judge to focus on an irrelevant issue—the *actual* safety and effectiveness of the WANS products.[28]

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[27] Actual safety and effectiveness will be resolved by the FDA in the context of its consideration of a new drug application for the WANS products. *See Equidantin Nitrofurantoin Suspension*, 675 F.2d at 1000 (and cases cited therein).

[28] The district court never fully appreciated the distinction between actual safety and effectiveness and general recognition of safety and

(*continued on following page*)

Dr. Barker is an FDA official who was intimately involved with the sequence of events that led to FDA's regulatory letter. Based on her testimony that fatal reactions had not in fact been reported, and on the court's willingness to receive it, the jury was misdirected from the real issue in the case—"general recognition" of safety and effectiveness—and concluded that the agency's decision to take enforcement action against the WANS and similar products had been predicated on their having caused fatalities. Moreover, the jury was erroneously led to believe that the government was now pursuing a mere technical violation. Because such a line of reasoning improperly enhanced the likelihood of the jury's verdict, the court committed reversible error.[29]

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(*Note continued*)

effectiveness. In denying the government's motion for judgment notwithstanding the verdict, the court stated "that defendants produced the medical reviewing officers from the Food and Drug Administration [Dr. Barker] who first originated documents questioning the safety of WANS. From such testimony, one can only conclude that the jury did not believe such allegations were supported by the facts disclosed at trial." [Order at 6] J.A. 646.

[29] In its Designation of Contents of the Appendix and Statement of the Issues on Appeal, the government designated the admission of Dr. Barker's testimony as a separate issue for appeal. The issue has not been treated separately in this brief because the government has concluded that the issue is subsumed in the issue concerning general recognition. Moreover, by virtue of this Court's granting of the Government's Motion for a Deferred Appendix, and pursuant to Rule 30(c), Fed. R. App. P., the issues stated in this brief supercede the issues stated in the Government's Designation of Contents of the Appendix and Statement of the Issues on Appeal.

APPENDIX M

(Reprinted from 1978 edition of Physicians' Desk Reference (PDR), p. 575)

EMESERT® Rectal Inserts

Description: EMESERT No. 1: Each PINK insert contains 25 mg. pyrilamine maleate, 30 mg. pentobarbital*; EMESERT No. 2: Each GREEN insert contains: 50 mg. pyrilamine maleate, 45 mg. pentobarbital*; EMESERT No. 3: Each BLUE insert contains: 50 mg. pyrilamine maleate, 100 mg. pentobarbital*; all in a water-soluble colored polyethylene glycol base.

*Warning: May be habit-forming.

Actions: A synergistic combination of an anti-nauseant, pyrilamine maleate, with a fast acting sedative, pentobarbital. Because the inserts are administered rectally, there is no gastric irritation or loss of medication. Absorption is rapid—effective between evacuations when diarrhea is present. The polyethylene glycol base is dissolved by the action of the rectal mucosal secretions, releasing the drugs for prompt absorption.

Indications: For the control of nausea and vomiting.

Contraindications: Hypersensitivity to barbiturates or antihistamines; acute intermittent porphyria; in patients with anorectal disease or severe hepatic impairment; in the presence of uncontrolled pain; acute head injury associated with vomiting or other signs of CNS trauma; known previous barbiturate addiction. Not recommended for use in infants under six months of age since they are more sensitive to the central nervous system stimulating effects of pyrilamine maleate than adults and thus, it may cause convulsions in infants, particularly in excessive dosage.

Warnings: The safety of Emeserts in pregnancy has not been established. Therefore, it is recommended that the

drug be given to women of childbearing potential and pregnant patients only when, in the judgement of the physician the potential benefits outweight the possible risks. Administration of Emeserts to patients with severe psychologic disturbances may result in confusion, delirium and accentuation of the condition. Concomitant use of alcohol or other central nervous system depressants may result in an additive effect and patients should be advised accordingly. Prolonged administration of barbiturates, even at doses contained in Emesert, may result in psychic dependence. Withdrawal symptoms may occur after large doses resulting in delirium, convulsions and death. Barbiturates are respiratory depressants. Caution is essential when the drug is administered in the presence of any respiratory difficulty.

Precautions: Administer with caution to patients with a history of drug dependence or suicidal tendencies. Due to the sedative effect, patients should be cautioned not to drive a car or to operate mechanical devices that require alert thinking. Emesert should be administered with caution to patients with hyperthyroidism, diabetes mellitus, severe anemia or congestive heart failure. Administer with caution in patients concurrently receiving other sedative, hypnotic or narcotic agents.

Adverse Reactions: Possible barbiturate adverse reactions include respiratory depression, allergic reactions, severe depression of the central nervous system, drowsiness, lethargy, hangover, paradoxical excitement, apnea and circulatory collapse. Possible antihistamine adverse reactions include tremor, dryness of mouth, nose and throat; tinnitus, pupillary dilitation, urinary retention, excitation, hypotension, palpitation, tachycardia, fatigue, vertigo, incoordination and muscle weakness.

Dosage and Administration:

Emesert #1: For children 6 months-2 years of age: one insert rectally, pointed end first. May be repeated every

6-8 hours. Do not exceed 3 doses in 24 hours. Use is not recommended in infants below the age of 6 months.

For children 2-12 years of age: one insert rectally, pointed end first. May be repeated every 6-8 hours. Do not exceed four doses in 24 hours.

Emesert #2: Older children (above age 12) and adults less severely affected: One insert rectally, pointed end first. May be repeated every 4-6 hours. Do not exceed four doses in 24 hours.

Emesert #3: Adults in cases of severe nausea and vomiting, one insert rectally, pointed end first. May be repeated every 6-8 hours. Do not exceed four doses in 24 hours.

Overdosage: Symptoms of overdosage are coma, diminished or absent reflexes, respiratory depression, hypothermia followed by fever and gradual appearance of circulatory collapse and pulmonary edema. Treatment consists of maintaining and assisting respiration as necessary; supporting circulation with vasopressors and intravenous fluids; dialysis, if indicated; aspiration of stomach contents (particularly if Emeserts are ingested); administration of osmotic diuretic and antibiotics as needed.

How Supplied: Box of 12 (strip-packed). Box of 50 (strip-packed).

APPENDIX N

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